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REVIEW OF

DISEASES OF THE THROAT

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SUMMARY

This review examines how the state of medical opinion about the alleged relationship between smoking and diseases of the throat has evolved since the middle of the nineteenth century. This task was based partly on the findings of the comprehensive review of the world literature on tobacco compiled by Larson, Haag and Silvette in 1961, and partly on an extensive review of the epidemiological evidence appearing since about 1950.

The throat is the cavity from the arch of the palate to the glottis and includes the pharynx and the larynx. Diseases of the throat range in severity from a sore throat to malignant neoplasms. Cancers of the larynx and pharynx are primarily diseases of old age, and are reported to be often curable.

It would appear that a case of laryngitis was attributed to smoking in 1867 and, some fifty years later, it was claimed that tobacco can cause throat cancer. In the 1930s it was stated that tobacco smoking was an etiological factor in cancer of the larynx although it was also said that there was no conclusive evidence that tobacco was injurious to the throat. Alcohol was first implicated as a factor in laryngeal cancer in 1936 and has been emphasised in many papers since then.

In the 1940s and 1950s papers appeared which said that smoking was not a significant factor, or that it had not been proved that smoking played a part, in cancer of the larynx. However, the major epidemiological studies conducted in the 1950s and 1960s alleged that cigarette smoking was a risk factor and that a dose-response effect was evident.

The first report on smoking by the Royal College of Physicians (RCP) published in 1962 did not refer to cancers of the mouth, larynx or pharynx, although the first United States Surgeon General's Report, in 1964, said that cigarette smoking was a significant factor in laryngeal cancer.

Major epidemiological studies have alleged that cigarette smokers have between about 3 and about 10, or more, times the risk of developing cancer of the larynx than non-smokers. Similar results have been alleged for cancer of the pharynx. Some epidemiological information has alleged that ex-smokers have a lower risk of laryngeal/pharyngeal cancers than current smokers.

However, a range of dietary and occupational factors have been implicated with cancers of the larynx and pharynx, a genetic influence has been suggested and numerous miscellaneous factors have been identified. The most frequently mentioned factor would seem to be alcohol, and it has been suggested that smoking and alcohol act together in a way to increase the risk of laryngeal

cancer. Dietary deficits have been implicated with increased risk, and it has been suggested that employment in selected occupations is associated with an increased laryngeal cancer risk. About 30 different alleged risk factors are noted in this review.

Over the years the RCP, the US Surgeon General, and the World Health Organization (WHO) have expressed their views on smoking and cancer of the throat. The latest view of the RCP is that these cancers have been shown to be associated with smoking. The Surgeon General goes one stage further, stating that cancers of the larynx and oral cavity are caused by smoking. The WHO states that there is an effect of tobacco smoking and a dose-response relationship. However, it has been claimed that, in the United Kingdom, time trends for laryngeal cancer follow changes in alcohol consumption rather than tobacco consumption.

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C O N T E N T S

1. INTRODUCTION

This document reviews the information available about the alleged relationship between smoking and certain diseases of the throat, with particular reference to cancers of the pharynx and larynx.

Section 2 of this document defines the throat and lists some of the diseases to which it is prone. These range in severity from a 'sore throat' which is usually caused by inflammation of the tonsils, larynx or pharynx, to cancers of part of the throat, such as the pharynx or larynx.

This document examines how the state of medical opinion has evolved over the years about the alleged relation between smoking and diseases of the throat. This has been primarily conducted using the major reference document (Larson, Haag and Silvette, 1961) which contains a comprehensive account of the world literature on "tobacco : experimental and clinical studies" going back to the middle of the nineteenth century. The conclusions of these reviewers are summarised in Section 3.

The views held in the 1960s and early 1970s by the Royal College of Physicians and the United States Surgeon General at around the time when health warnings were introduced on cigarette packets are summarised in Section 4. These views were based primarily on the epidemiological studies conducted in the 1950s and 1960s that were also referred to by Larson, Haag and Silvette.

Section 5 reviews in detail the epidemiological studies which have been conducted in the last thirty years or so.

Section 6 identifies other factors, such as environmental exposure, which have been implicated in the etiology of laryngeal and pharyngeal cancer.

Section 7 summarises the current standpoint of official organisations such as the World Health Organization, the Royal College of Physicians or the United States Surgeon General. Comments made by other reviewers are included in this section.

Section 8 summarises the main points made in the review.

2. DEFINITION OF AND DISEASES OF THE THROAT

Definition of the Throat

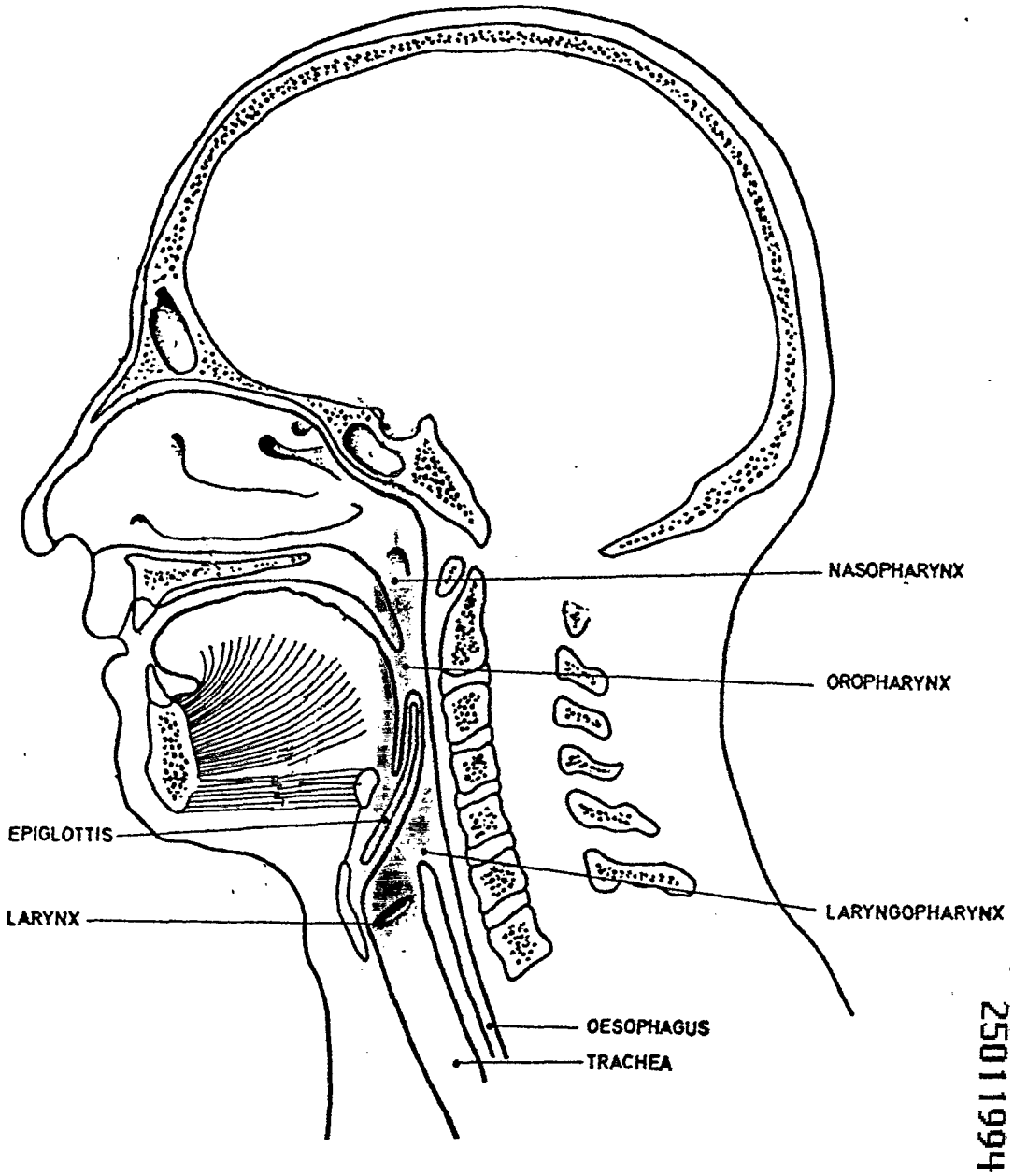
Taber's Cyclopedic Medical Dictionary defines the throat as follows:

1. The pharynx and the fauces (i.e. aperture leading from mouth into pharynx).

2. Cavity from arch of palate to glottis and superior opening of the oesophagus.

3. The front of the neck.

The Figure below shows a section of the head and neck and throat. The throat, which is the pharynx, the larynx and the epiglottis, has been highlighted in yellow below.



The various components of the throat are defined as follows:

Pharynx	- tube extending from base of skull to oesophagus
Nasopharynx	- upper portion of the pharynx
Oropharynx	- lower portion of pharynx
Epiglottis	- thin structure which covers the larynx when swallowing
Laryngopharynx	- boundary between pharynx and larynx
Larynx	- upper end of trachea; the organ of voice

Diseases of the Throat

Passmore and Robson (1974) state that the mucous membranes of the throat are commonly involved in infections that may be either endogenous or airborne in origin and follow an acute or chronic course. The throat can also be the seat of benign and malignant neoplasms.

Passmore and Robson (idib) also list the diseases of the nasopharynx and larynx as follows:

Nasopharynx:

- adenoids
- tumours of the nasopharynx
- infection and ulceration of the pharynx

Larynx:

- acute epiglottis
- acute laryngitis
- acute laryngeal stridor
- oedema of the glottis
- chronic laryngitis
- tuberculous larynx
- syphillitic laryngitis
- laryngeal polyp
- vocal nodules
- keratosis of the larynx
- laryngeal paralysis
- tumours of the larynx
- swellings in the neck

This review will be restricted mainly to malignant neoplasms of the larynx and pharynx. Many of the other diseases of the throat are either very rare or are children's diseases. For some of the diseases epidemiological data is not available. However, for the purposes of completeness, and to assist the interested reader, the relevant pages from Passmore and Robson detailing the above diseases are shown in Appendix 1.

Cancers of the oral cavity and pharynx are often grouped together for classification purposes. More than 90% of all oral and pharyngeal cancers occur in patients over 45 years of age. Incidence increases steadily with age, with a sharp rise in the 60-64 age group (Mahboubi and Sayed, 1982). Table 1 illustrates the worldwide variation in incidence rates from the highest of 33.2 per 100,000 in Bombay, India, to the lowest of 1.3 in non-Jewish females in Israel.

TABLE 1. Age-Adjusted Incidence Rates Per 100,000 for Cancer of Oral Cavity and Pharynx in 23 Populations, Highest and Lowest Rates by Rank, Sex, and Male to Female Ratio, 1968–1972*

Country	Rank for Males	Rate MALE	Rate FEMALE	Sex Ratio M/F
Bombay, India	1	33.2	12.1	2.7
Puerto Rico, U.S.	2	25.9	6.9	3.8
São Paulo, Brazil	3	24.3	4.8	5.1
Singapore (Indian)	4	22.1	25.5	0.9
El Paso, U.S. (White)	5	21.3	5.8	3.7
Quebec, Canada	6	15.3	3.7	4.2
Alberta, Canada	7	15.2	2.7	5.6
Cuba	8	14.6	3.8	3.8
Geneva, Switzerland	9	14.2	3.0	4.7
Connecticut, U.S.	10	13.1	4.4	3.0
Detroit, U.S. (White)	11	11.3	3.8	3.0
Detroit, U.S. (Black)	12	11.2	4.1	2.7
Saarland, Federal Republic of Germany	13	11.2	2.9	3.9
New York State, U.S.	14	10.2	3.2	3.2
Hamburg, Federal Republic of Germany	15	9.0	3.3	2.7
Israel (All Jews)	16	7.4	3.4	2.2
Israel (Non-Jews)	17	7.1	1.3	5.5
Singapore (Chinese)	18	6.9	1.7	4.1
Sweden	19	6.2	2.4	2.6
Oxford, U.K.	20	6.1	1.8	3.4
Singapore (Malay)	21	6.0	1.6	3.8
El Paso, U.S. (Spanish)	22	4.6	6.2	0.7
Ibadan, Nigeria	23	4.2	3.2	1.3

*From Waterhouse et al (1976).

Cancer of the larynx was rarely diagnosed until about 1860 after the invention of the laryngoscope (Austin, 1982). Cancer of the larynx also varies in incidence worldwide, but invariably predominates in males. Laryngeal cancer represents about 2.3% of all cancer in males in the United States (Austin, 1982). Males and females of Bombay, India, rank among the highest in the world for laryngeal cancer (13.6 and 2.6 per 100,000, respectively). Cancer of the larynx is primarily a disease of old age, the median age usually cited being in the sixth or seventh decade (Austin, 1982).

3. EVOLUTION OF KNOWLEDGE, 1839 - 1959

Relevant extracts from the major review on "tobacco: experimental and clinical studies" (Larson, Haag and Silvette, 1961) have been re-assembled in chronological order in Appendix 2. The main conclusions are summarised below:

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According to Larson, Haag and Silvette:

- In 1839 it was inferred that smoking or chewing of tobacco kept up a secretion in the neighbourhood of the glottis, favourable to the good condition and healthy action of the vocal box. These observations caused "a storm of controversy".

- In 1846 it was reported that "many an irritable nervous cough ... have I known to follow the frequent use of tobacco".

- A case of laryngitis was attributed to smoking in 1867. A report of chronic pharyngitis kept up by excessive smoking was cited in 1885.

- It was recommended in 1894 that smoking be stopped in all diseases of the larynx and pharynx.

- In 1904 it was claimed that tobacco was harmful to the throat.

- In 1910 it was stated that there was not one scintilla of evidence that malignant disease of the throat was due in any way to the use of tobacco.

- It was stated in 1916 that tobacco can cause throat cancer.

- In 1929 it was stated that most inveterate smokers show some congestion of the pharynx regardless of the brand of tobacco smoked.

- In the 1930s the belief was expressed that tobacco smoking is an etiological factor in the development of cancer of the larynx. This view has been expressed subsequently.

- In 1931, it was stated that there was no conclusive evidence that tobacco was injurious to the throat.

- In 1935 it was alleged that excessive use of tobacco was probably a predisposing cause of a number of cases of cancer of the larynx.

- It was noted in 1936 that those occupied in supplying alcohol showed a much higher incidence of laryngeal than lung cancer.

- It was alleged in one study in 1936 that there was a 98% incidence of tobacco use in 233 cases of cancer of the oral cavity, larynx, pharynx and oesophagus.

- Vocal abuse was considered a predisposing or contributing cause of cancer of the larynx in 1935.

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- In 1943, it was stated that it had not been proven that smoking plays a part in cancer of the larynx.

- In 1950, it was stated that smoking per se was not one of the significant etiologic factors in cancer of the larynx.

- In 1955 it was alleged that cigarette-smoking alone could be held responsible for the increase in laryngeal cancer among males.

- In 1956 it was alleged that the risk of developing cancer of the larynx increased with the amount of tobacco consumed.

- Hoarseness, chronic cough, having no teeth and exposure to strong heat at work were said, in 1956, to be related to cancer of the larynx.

- The alleged influence of heavy alcohol consumption as one of the factors in laryngeal cancer was emphasised in the 1950s.

- Significant relationships to smoking were reported in Sweden in 1957 for cancer of the larynx (in cigarette and cigar smokers) and upper hypopharynx (in cigarette smokers).

- In 1957, it was alleged that in a series of 102 histologically proved cases of cancer of the larynx, 100 were habitual smokers, almost exclusively of cigarettes.

4. VIEWS OF THE ROYAL COLLEGE OF PHYSICIANS AND THE UNITED STATES SURGEON GENERAL IN THE 1960s AND EARLY 1970s

Royal College of Physicians (1962)

The first (1962) Royal College of Physicians (RCP) on "Smoking and Health" did not refer to cancers of the mouth, larynx or pharynx.

Surgeon General (1964)

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Laryngeal Cancer

The 1964 Report of the United States Surgeon General (SG) stated that "the possible association between tobacco smoking and laryngeal cancer received some attention in studies as early as 1937 (Ahlborn, 1937; Kennaway and Kennaway, 1937)". However, the SG stated that "it is difficult to attach much importance to these studies though they contain clues which should be investigated". The SG commented that the earliest "controlled study" (that of Schrek and co-workers in 1950) "showed an association between smoking and cancer of the larynx but the evidence is not firm for the association was found in only one out of four age groups".

The SG reviewed virtually the same retrospective studies as those discussed by Larson, Haag and Silvette (i.e. Sadowsky, Gilliam and Comfield, 1953; Blumlein, 1955; Dutta-Choudhuri, Roy and Gupta, 1959; Schartz, Denoix and Anguera, 1957; Wynder, Bross and Day, 1956; Wynder et al, 1957; Wynder et al, 1958). The SG also reviewed seven prospective studies (Best, 1961; Doll and Hill, 1954; Dunn, Linden and Breslow, 1960; Dunn, Buell and Breslow; Hammond; Dorn, 1959; Hammond and Horn, 1958) and concluded that "a summation of all seven

studies yields a mean mortality ratio of 5.4 for cigarette smokers", relative to non-smokers. The SG estimated that the risk ratio rose from "5.3 for smokers of one pack or less of cigarettes per day to 7.5 for smokers of more than a pack a day".

The SG noted that "other factors may play a significant role in the production of laryngeal cancer, such as alcohol and inadequate nutrition (Wynder, Bross and Day, 1956). For instance, the SG stated that the incidence of laryngeal cancer was higher in males than in females and pointed out that "the greater alcohol consumption among males and a strong association between laryngeal cancer and alcohol consumption (Wynder, Bross and Day, 1956; Wynder, Bross and Day, 1956) must be considered as contributing to the excess ratio of male to female laryngeal cancer mortality".

The conclusion drawn by the SG was that "evaluation of the evidence leads to the judgement that cigarette smoking is a significant factor in the causation of laryngeal cancer in the male".

Pharyngeal Cancer

The SG noted that most of the studies on oral cancer had considered combinations of specific sites and hence in only four studies was pharyngeal cancer considered as a separate site (Sadowsky, Gilliam and Comfield, 1953; Sanghvi, Rao and Khanolkar, 1955; Wynder, Bross and Feldman, 1957; Wynder, Huttberg, Jacobsson and Bross, 1957). The SG said that an association with smoking was "noted in two" of the studies.

Surgeon General (1967)

The 1967 Report of the SG on the Health Consequences of Smoking reviewed the research studies published since 1964. New reports of four major epidemiological studies had been published which provided (i) an extension of the time period of follow-up, (ii) additional data on specific age groups, and (iii) data on women (Best, 1966; Doll and Hill, 1964; Doll and Hill, 1964; Doll and Hill, 1966; Hammond, 1966; Kahn, 1966). The SG drew the following conclusion on laryngeal cancer:

> "Continued evidence from the prospective studies supports the existence of a high laryngeal cancer mortality ratio for pipe and cigar smokers as well as for cigarette smokers. Data on the smoking habits of patients treated for buccal cancer subsequent to their therapy suggests that continuing to smoke after therapy may increase the likelihood of an independent laryngeal cancer. The epidemiological evidence supports the previous conclusion that cigarette smoking is a significant factor in the causation of cancer of the larynx."

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On oral cancer, the conclusion was as follows:

"Substantial mortality ratios are found in cancers of the buccal cavity and pharynx. Mortality ratios for cancer of the pharynx are especially high. There is some evidence implicating alcohol and/or dietary deficiencies in some of these sites. With the exception of the pipe-lip cancer relations there are too few cases related to the individual parts of the buccal cavity to evaluate each independently, and data are inadequate on the interaction of smoking with other factors. Although all forms of smoking have high mortality ratios with these sites, mortality ratios for those smoking cigarettes appear to be somewhat higher than for those smoking pipes and cigars, especially in the case of cancer of the pharynx."

Royal College of Physicians (1971)

The 1971 RCP Report "Smoking and Health Now" contained a paragraph on smoking and cancer of various organs. It was stated that "an association of cancers of the mouth, pharynx, larynx, and the oesophagus with smoking of cigarettes or of pipes and cigars has been shown by several investigations (Doll and Hill, 1964; Hammond, 1966; Kahn, 1966; US Public Health Service, 1964; US Public Health Service, 1967),and pre-cancerous changes in the larynx and oesophagus have been observed more often in men who had smoked than in non-smokers (Auerbach, Stout and Hammond, 1965; US Public Health Service, 1969). In Dorn's prospective study of American veterans mortality from these cancers was directly related to the number of cigarettes smoked (Kahn, 1966); since, however, in respect of cancer of the mouth and larynx there is also an association with heavy drinking (Wynder, Bross and Day, 1956; Wynder, Bross and Feldman, 1957), alcohol may also contribute to their causation. Although these cancers are not uncommon they are often curable and make a small contribution to the excess mortality of cigarette smokers compared with non-smokers."

The RCP concluded that "cancers of the mouth, larynx and oesophagus are more frequent in smokers of all kinds of tobacco than in non-smokers".

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Surgeon General (1971)

The 1971 Report of the United States Surgeon General concluded that "epidemiological, experimental, and pathological studies support the conclusion that cigarette smoking is a significant factor in the causation of cancer of the larynx. The risk of developing laryngeal cancer among cigarette smokers as well as pipe and/or cigar smokers is significantly higher than among nonsmokers. The magnitude of the risk for pipe and cigar smokers is about the same order as that for cigarette smokers, or possibly slightly lower".

On cancers of the oral cavity the Surgeon General concluded that "epidemiological and experimental studies contribute to the conclusion that smoking is a significant factor in the development of cancer of the oral cavity".

5. EPIDEMIOLOGICAL EVIDENCE ON SMOKING AND CANCER OF THE LARYNX AND PHARYNX

Introduction

Sections 3 and 4 briefly referred to the epidemiological studies on diseases of the throat. Two types of study have been conducted. In a prospective study a group of individuals, such as ex-servicemen or ex-students, are interviewed and then followed up over many years. The deaths which occur are recorded, and contrasted with information collected at the original interview on certain aspects of lifestyle such as drinking or smoking habits, place of residence, socio-economic status, etc. In this way it is possible to calculate mortality rates for various diseases, for different types of individual.

In this paper, the most frequently used comparison will be the mortality ratio of smokers to non-smokers. If, for instance, the alleged ratio is 2.0 this means that the study reported that smokers experienced twice the mortality from that disease compared with non-smokers. If the ratio is less than 1, this means that smokers were reported to experience less mortality than non-smokers.

In a retrospective study, a group of patients with a particular disease, such as laryngeal cancer, are identified and then contrasted with a group of patients without that disease, who are known as the 'control' group. Sometimes the 'control' group are free of all disease, and are selected in such a way as to 'match' the age, sex and socio-economic status of the disease group. The smoking habits, or drinking habits of two groups are then compared and the mortality ratio is calculated in a similar way. For instance, a mortality ratio of 3.5 for liver cirrhosis for drinkers would mean that drinkers experienced three and half times the mortality rate from this disease than did non-drinkers.

Some of the studies use the term 'relative risk' to contrast smokers with non-smokers. This concept is essentially the same as that of mortality ratio.

Sometimes the 'disease' group and the 'control' group differ in terms of some factor which may influence their mortality experience, such as age. The mortality ratios, or relative risk calculations, are, therefore, 'age standardised' using a statistical technique to eliminate the effect of this variable. In some studies the results are also standardised for other factors, such as socio-economic level.

The main prospective studies were carried out in the 1950s and 1960s, and numerous smaller scale retrospective studies have been conducted in more recent years. The main prospective studies are considered in chronological order below:

PROSPECTIVE STUDIES

British Doctors Study (1950, 1952, 1954 and 1956)

The first two reports of the follow-up study of British doctors published in 1950 and 1952 did not refer to laryngeal or pharyngeal cancer - these early reports were confined to lung cancer.

The 1954 report by Doll and Hill referred to other disease groups but simply noted that the numbers of deaths for "some potentially interesting diseases are yet small (for example cancer of the buccal cavity and larynx and from duodenal ulcer)" to show "whether there is any relationship between smoking and mortality" from these diseases.

The 1956 report by Doll and Hill gave details of deaths from cancers of sites other than the lung. Thirteen doctors were reported to have died from cancer of the "upper respiratory and upper digestive tracts" since 1951. Doll and Hill reported that no death occurred among non-smokers (from this group of diseases) and that "the highest death rate occurred among heavy smokers, but the total number of cases is at present too small to give reliable results". [NB: It was clearly not possible to calculate a mortality ratio for smokers to non-smokers because all of the deaths from this group of cancers were reported to have occurred in cigarette smokers.]

American Cancer Society's Study (1958)

Hammond and Horn collected data on nearly 200,000 men in the USA aged 50-69 and followed them up during 1952-55. Although 24 deaths occurred from cancer of the larynx it was reported that they all occurred in smokers. Clearly this made calculation of the mortality rate impossible.

British Doctors Study (1964)

Doll and Hill's paper reported on ten years observations on British doctors. Nineteen men had died of cancer of the mouth, pharynx or nose and 16 of larynx or trachea in that period. The authors recognised that those numbers of deaths were "very small" but nevertheless they reported that the death rates for these cancers "are higher in smokers than in non-smokers, but they are not specifically higher in cigarette smokers than in other smokers". Doll and Hill stated that they had "too few deaths" to examine each of the cancer sites separately, but claimed that their results for cancers of the upper respiratory and digestive tracts "agree with those of other studies and indicate that these cancers are about five times as common in smokers as in non-smokers". Doll and Hill continued "whether this observation should be interpreted to mean that such cancers are caused by smoking is, however, open to doubt".

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US Veterans Study (1966)

Kahn reported another large scale prospective study in the USA in which 248,000 male insurance policyholders aged between 35 and 84, most of whom were veterans of World War I had been followed up for 8.5 years. Fifty four deaths from laryngeal cancer occurred, and the mortality ratio for smokers to non-smokers was reported as 9.95. Kahn did not report results for cancer of the pharynx.

American Cancer Society's Study (1966)

Hammond published the results of the American Cancer Society's study on over one million men and women between the ages of 35 and 84 who had been traced at least once during the four-year period 1959-63. Mortality ratios for cigarette smokers relative to never-smokers were reported as follows:

	Mortality Ratios		
	Men		Women
Cause of Death	Age 45-64	Age 65-79	Age 45-64
Cancer of buccal cavity, pharynx	9.90	2.93	*
Cancer of larynx	6.09	8.99	*
Buccal cavity, pharynx, and oesophagus			1.79

* Not reported separately

California Union Members (1970)

Weir and Dunn reported the mortality experience of 68,153 male union members aged 35-64 over a period of seven years. The reported relative risk for cancer of the pharynx was less than 1, i.e. 0.76. The study was unable to calculate a corresponding value for cancer of the larynx because "there were no nonsmokers dying of cancer of the larynx".

Japanese Study (1975)

Hirayama reported 31 male laryngeal deaths in his follow-up study of 172,261 males over eight years in Japan. The alleged relative risk for cigarette smokers was 13.59.

Karolinska Institute Study (1975)

A ten-year follow-up study on 55,000 Swedish subjects aged 18-69 was published in 1975. It was reported that no deaths occurred among male non-smokers from cancer of the larynx, and that no females died from this disease. This means, of course, that it is impossible to calculate odds-ratios.

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British Doctors Study (1976)

In 1976, Doll and Peto published the results of 20 years observations on their study of doctors. Cancers of the "lip, tongue, mouth, pharynx (excluding nasopharynx), larynx, and trachea were classified together as 'upper respiratory cancers' because numbers of deaths attributed to individual types were too few". Forty six deaths occurred, and the annual death rates were reported as follows:

	Per 100,000
Non-smokers	1
Cigarettes only	13
1-14 cigarettes/day	5
15-24 cigarettes/day	7
>25 cigarettes/day	33

Doll and Peto stated that cancers of "other respiratory sites ... have been known to be associated with smoking for many years" and "our present data reinforce earlier conclusions".

Third National Cancer Survey (1977)

Williams and Horm reported a study of 7,518 patients in the Third National Cancer Survey in the United States. Cigarette consumption levels were represented by cigarette usage in terms of pack years. The reported odds ratios for cancers of the pharynx and larynx were as follows:

	Males			Females		
	Pack years			Pack years		
	<20	20-39	40+	<20	20-39	40+
Pharynx	1.82	3.21*	4.77**	1.44	2.79	11.12***
Larynx	2.90	3.31*	17.66***	5.96	-	22.32

* p <.05, ** p <0.01, *** p <.001

The authors also reported significantly elevated relative risks for both pharyngeal and laryngeal cancers among wine, beer and hard liquor users compared with non-drinkers. The relationship between tobacco, alcohol and other factors, such as socioeconomic status, and cancer of the pharynx and larynx is discussed in detail in Section 6.

US Veterans Study (1980)

Rogot and Murray reported the results after 16 years of follow-up (1954-1969) in the study of US Veterans which had been reported after 8.5 years by Kahn in 1966. The alleged relative risks for male cigarette smokers were as follows:

Cancer of the pharynx	14.05
Cancer of the larynx	11.49

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US Cancer Prevention Study II (1989)

The American Cancer Society initiated a new study in September, 1982. This has been named CPS-II, and some "preliminary results of the first 4 years of follow-up (1982-86) are available" (US Department of Health and Human Services, 1989). Over 1.2 million persons in the USA were enrolled. The alleged relative risks for male smokers aged 35 years or more were as follows:

Cancer of the larynx	10.48
Cancer of lip, oral cavity and pharynx	27.48

Summary of Prospective Studies

The mortality ratios for male smokers relative to male non-smokers which have been reported in the above studies are summarised below:

	Cancer of Larynx	Cancer of Pharynx
British Doctors	13.0[1]	
American Cancer Society	6.09[2]	9.90[2]
US Veterans	11.49	14.05
Californian Union Members	*	0.76
Japanese	13.59	
Karolinska	*	
Third National Cancer	>2.90	>1.82
CPS-II	10.48	27.48

Notes:

* All deaths occurred in non-smokers
1 Includes cancer of the larynx and upper respiratory tract
2 Males aged 45-64

It will be seen that the alleged mortality ratios for laryngeal cancer for males are not very consistent; they range from about 3 to 14. For cancer of the pharynx, where less information is available, the alleged rates show an even larger range. However, one of the studies reported a negative association.

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RETROSPECTIVE STUDIES

The 1982 Report of the US Surgeon General claimed that "more than 25 retrospective studies have examined the relationship between smoking and laryngeal cancer. These studies have employed diverse methodology and have been performed in different time periods and in different countries. Regardless of the study design, these studies have found a positive association between smoking and cancer of the larynx".

It is not proposed to review all the retrospective studies which have been reported but instead an attempt has been made to summarise a sample of these studies, particularly some of the older ones.

Summary of Retrospective Studies

The mortality ratios for laryngeal cancer reported in retrospective studies which were published in the 1950s are summarised below:

Investigator	Year	Country	Number of Cases	Number of Controls	Ratio
Schrek	1950	USA	73	522	2.0
Valko	1952	Czech	226	108	3.5
Sadowsky et al	1953	USA	273	615	3.7
Blumlein	1955	Germany	241	200	27.5
Wynder et al	1956	USA	209	209	23.6
Wynder et al	1956	India	132	132	3.1
Schwartz et al	1957	France	121	242	4.6
Wynder et al	1957	Sweden	63	271	6.0
Wynder et al	1958	Cuba	142	220	18.9

Most of these studies were based on men. However, it must be stressed that some of the studies were based on small numbers of deaths from laryngeal cancer amongst non-smokers. This may partly explain why the reported relative risks range from 2.0 to 27.5.

As far as cancer of the pharynx is concerned, some retrospective studies have included this site in a category of oral cancer, which includes lip, tongue, mouth, palate, gums, buccal mucosa and oropharynx. Clearly many of these sites fall outside the definition of the throat. However, an attempt to summarise the retrospective information on oral cancer which was published in the 1950s has been made below. The 'result' column assesses the cigarette smoker : non-smoker mortality ratio:

Investigator	Year	Country	Number of Cases	Number of Controls	Result
Mills & Porter	1950	USA	124	185	0
Sadowsky et al	1953	USA	1136	615	-
Ledermann	1955	France	240	62	+
Schwartz et al	1957	France	332	608	+
Wynder et al	1957	USA	543	207	0
Wynder et al	1957	Cuba	178	220	-
Wynder et al	1957	Sweden	255	271	+

Key: 0 Association of doubtful significance
- Association absent or not significant
+ Significant association

Clearly the results of these studies are inconclusive. It is important that the 1964 Surgeon General's Report concluded that "although there are suggestions of relationships between cancer of other specific sites of the oral cavity and the several forms of tobacco use, their casual implications cannot at present be stated".

2501199424

Giving up Smoking

A few studies have reported on the relationship between giving up smoking and cancers of the larynx and pharynx. In the 16-year follow-up of US Veterans (Rogot and Murray, 1980) the reported relative risk of laryngeal cancer for male ex-cigarette smokers was 4.78 compared with 11.49 for male current cigarette smokers. In Doll and Peto's 1976 paper reporting 20 years observations on British doctors the ex-smokers mortality rate per 100,000 from 'upper respiratory cancers' was 4 (compared with 1 per 100,000 for non-smokers) and 13 for current smokers. Wynder and Stellman (1979) stated that "10-15 years of cessation are required before the long-term smoker's risk" - i.e. of lung or larynx cancer - "approaches that of a non-smoker".

Moore (1964) reported a follow-up study of 78 smokers who had been "cured" of mouth-throat cancer. After a mean follow-up period of 6.7 years, it was claimed that "17 of 49 of those who continued to smoke developed a second mouth-throat cancer, while only one of 29 who had quit smoking developed a second cancer".

6. FACTORS IMPLICATED IN LARYNGEAL AND PHARYNGEAL CANCER

The epidemiological studies have identified a range of factors other than cigarette smoking in cancers of the larynx and pharynx. It is worth bearing in mind the comment made in 1982 by Heath that since "cancers generally are of multifactorial etiology it is impossible to know which particular case results from which particular cause or set of causes".

The factors identified in laryngeal and pharyngeal cancers include dietary and occupational factors, genetic influence as well as other miscellaneous factors. The evidence is summarised below:

Dietary Factors

Alcohol

By far the most frequently reported relationship is that of alcohol consumption and laryngeal cancer. As noted in Section 3, Kennaway and Kennaway (1936) found that those occupied in supplying alcohol showed a much higher increase over 1921-32 of laryngeal than of lung cancer. The influence of alcohol consumption as a factor in laryngeal cancer has been pointed out by many authors over the last 30 years. For instance, Wynder, Bross and Day (1956) noted that there are "two principal difficulties" in examining "the striking relationship of larynx cancer to tobacco and alcohol". They continued "first of all there are various aspects of tobacco and alcohol consumption to be considered" (i.e. amount, type, duration, etc.). The second "difficulty is that the alcohol and tobacco habits may be associated, and, consequently, considering the factors separately can give a misleading picture". The authors grouped their subjects into five smoking categories (non-smoking, pipe and cigar smokers,

cigarette smokers of 1-15, 16-34 and 35+ cigarettes per day, and five drinking categories (non-drinkers, beer/wine, whiskey, drinking of less than one, one to six, or seven plus 'shots' a day). The study reported:

- "a clear association between tobacco smoking and cancer of the larynx"
- "heavy alcohol consumption is demonstrated as an important variable among larynx-cancer patients"
- "the risk of larynx cancer rises proportionally with the amount of tobacco consumed. Such a proportional increase is not noted for alcohol consumption".

Williams and Horm (1977) reported a study of 7,518 patients in the Third National Cancer Survey in the United States. The reported odds ratios relative to non-drinkers, for cancers of the larynx and pharynx, by type and level of drinking habit were as follows:

	Wine Level		Beer Level		Hard Liquor Level	
	1	2	1	2	1	2
Males						
Pharynx	2.93	10.93***	2.69	9.93***	1.01	7.21***
Larynx	2.66	2.40	3.52**	3.49***	2.45*	2.82***
Females						
Pharynx	6.14	6.08	12.13	3.09	1.20	16.87***
Larynx	2.21	3.99	3.45	8.29	0.98	1.64

* p <.05, ** p <.01, *** p <.001

The authors stated that "the intake of alcoholic beverages was positively associated with large and consistent dose-response increases for cancer of the oral cavity and larynx". However, when the results were standardised for smoking habits the relative risks generally reduced, as shown below:

Relative odds controlling for smoking:

	Wine Level		Beer Level		Hard Liquor Level	
	1	2	1	2	1	2
Males						
Pharynx	1.90	17.70**	3.06	10.28**	1.24	5.90**
Larynx	2.13	2.16	3.66**	3.03**	2.22	2.23*
Females						
Pharynx	3.03	4.74	7.61	2.83	1.10	24.61**
Larynx	1.63	1.62	-	4.35	0.52	1.00

2501199426

The authors commented "that the association of alcohol with cancer sites has not been studied as extensively as the association with smoking". They noted that there was evidence of "a co-operative role between tobacco and alcohol" and said that future studies should include "in-depth analyses of synergism".

A recent paper (Guenel et al, 1988) stated that "previous studies of the interaction between alcohol and tobacco in cancer of the larynx generally concluded that there was more than an additive effect, i.e. an effect of combined exposure to both agents which was greater than the sum of the effects due to each agent alone". Sarracci (1987) concluded that the "interaction appears consistently multiplicative for laryngeal cancers". This view was supported by Tuyns et al (1988), based on studies in Spain, Italy and Switzerland.

Several authors postulated a biological mechanism to account for the alleged interaction. Flanders and Rothman (1982) said that there may be "physical contact between alcohol and the tobacco carcinogens, perhaps with the alcohol acting as a solvent and thereby facilitating entry of tobacco carcinogens into epithelial cells". McCoy and Wynder (1979) suggested that alcohol may affect metabolism of the laryngeal epithelium, or that it affects metabolic conversion of carcinogens in the liver. Brownson (1988) suggested that "since alcohol is not considered singly carcinogenic, it is possible that tobacco serves as an initiator and alcohol a promoter in laryngeal carcinogenesis".

Vegetables and Fruits

Stefani et al (1987) reported a case-control study of laryngeal cancer in Montevideo, Uraguay. They found "a moderate risk associated with infrequent consumption of vegetables" which "replicated previous findings of Graham" (1981). Stefani et al said that the relative risk "was higher for infrequent fruit consumption. These findings suggest that dietary deficits play a role in the causation of laryngeal cancer in Uraguay".

McLaughlin et al (1988) carried out a case-control study of oral and pharyngeal cancer in four areas of the United States. They reported that the "major finding" was "an inverse relationship between fruit intake and risk of oral and pharyngeal cancer". The authors did state that "it is not clear what constituents of fruit may be responsible for lowering the risk of oral cancer".

Fat

Byers et al (1988) compared tobacco, alcohol and dietary histories of 250 laryngeal cancer cases with those of matched controls. They reported that the risk of laryngeal cancer was increased in persons in the highest of four fat consumption groups.

Vitamin A

Graham et al (1981) conducted an interview study with 374 patients with cancer of the larynx and 381 controls at an American hospital. The authors reported that males ingesting low amounts of vitamin A in their diet had approximately twice the risk (of cancer of the larynx) of those ingesting large amounts.

Carotene Intake

Mackerras et al (1988) reported a case-control study of laryngeal cancer in Texas. Dietary interviews were obtained with 151 living cases and 178 living controls. It was reported that "a significant inverse association (odds ratio (OR) = 2.1) was found between low carotene intake and the risk of laryngeal cancer, but no association was found with total vitamin A or retinol intake".

Occupational Factors

Asbestos

Several authors have reported an increased risk for laryngeal cancer among workers exposed to asbestos. For instance, Shettigara and Morgan (1975) concluded from a case-control study that "the data indicate a substantial association between asbestos exposure and laryngeal cancer". The authors noted that Newhouse and Berry suggested that "short exposure to asbestos may be a feature of laryngeal carcinoma". However, a recent review (Edelman, 1989) concluded that "neither case-control nor cohort studies have established an increased risk of laryngeal cancer for asbestos workers".

2501199428

Mustard Gas

Manning et al (1981) traced 84% of 511 men and women who manufactured mustard gas during the 1939-45 war. Seven workers who had been employed at a factory in Liverpool were known to have developed cancer of the larynx. The authors compared this observed number of patients with the disease with the expected number calculated from the age-specific incidence rates recorded by the Liverpool Cancer Registry. The ratio of the observed and expected numbers of cases (i.e. 0.75) was very highly statistically significant ($p < .001$), and the authors concluded that "the results of our study provide strong evidence that exposure to mustard gas produced a definite and substantial elevation in the risk of laryngeal cancer".

Easton, Peto and Doll (1988) carried out a much larger study of 2,498 men and 1,032 women employed in the manufacture of mustard gas in Cheshire during the second world war. They reported that "large and highly significant excesses were observed as compared with national death rates for deaths from cancer of the larynx". The authors said that their "results provide strong evidence that exposure to mustard gas can cause cancers of the upper respiratory tract".

Nickel

Pedersen, Hogetveit and Andersen (1973) reported a follow-up study of 1,916 men employed at a nickel refinery in Norway. Observed numbers of cases of laryngeal cancer were compared with expected numbers, based on Norwegian Cancer Registration data. Five deaths were recorded from cancer of the larynx, compared with an expected number of 1.4. The authors said that their results "permit no firm conclusions but do suggest that this", i.e. working at a nickel factory, "may be another manifestation of risk due to occupational exposure".

Olsen and Sabroe (1984) reported a case-control study of laryngeal cancer in Denmark. They stated that "exposure to nickel had a statistically significant risk ratio of 1.7".

Paint

Englund (1980) conducted a study in Sweden of cancer incidence among painters and some allied trades. They reported that amongst painters there was an almost threefold excess of deaths from cancer of the larynx.

Welding

Olsen et al (1984) conducted a case-control study of cancer of the larynx in Denmark, with particular reference to exposure to welding. They reported that "men exposed to welding fumes at their workplace had a borderline statistically significant risk of getting cancer of the larynx".

2501199429

Diethyl Sulphate and Sulphuric Acid

Lynch et al (1979) reported a morbidity and mortality study of workers at an alcohol manufacturing plant in Baton Rouge, Louisiana. They found that "the observed number of laryngeal cancer cases in a cohort of alcohol process workers was five times greater than expected". The authors speculated "it appears likely from the data that diethyl sulfate was the primary carcinogen responsible for the excess of upper respiratory cancer among ethanol workers".

In 1984, Soskolne et al published the results of a second study at the chemical plant in Baton Rouge. This study was initiated because cases of upper respiratory cancer, which had appeared to be confined to individuals on a strong acid ethanol process, i.e. Lynch et al's study, subsequently were observed in workers with no history of ethanol unit exposure. The results of the new study were "consistent with the findings" of the first study but, however, "do suggest a further interpretation that sulfuric acid exposure itself, notwithstanding the role of other possible carcinogenic agents, may be a major risk factor in the development of upper respiratory cancer in the industrial population studied". [NB: When sulphuric acid is used to manufacture ethanol, diethyl sulphate is formed in the process. Lynch et al thought that diethyl sulphate was the carcinogen involved in laryngeal cancer, whereas Soskolne et al considered that sulphuric acid was the factor.]

Acid Mists

A study was conducted (Steenland et al, 1988) to determine the relation between exposure to acid mist and the incidence of laryngeal cancer in 879 male steelworkers in three American steel mills. The authors reported that the "exposed" group "experienced an approximately 2.3-fold excess of laryngeal cancer compared with the United States referent population". They noted that their results were "consistent with four other studies published since 1981".

Metal Electroplating Industries

Blair and Mason (1980) conducted a survey of cancer mortality from 1950 to 1969 in US counties where greater than 0.1% of the county's population was employed in the metal electroplating and coating industry. They reported "higher mortality from cancers of the esophagus and larynx among males in the plating counties" compared with males in "control counties".

Other Work-related Factors

Flanders and Rothman (1982) studied the effects of type of employment on laryngeal cancer using the interview data from the Third National Cancer Survey (see page 12). They reported ratio estimates above 3.0 for the following groups:

- workers in the railroad industry
- workers in the lumber industry
- sheet metal workers
- grinding wheel operators
- automobile mechanics.

Flanders and Rothman stated that published reports suggest an increased risk for laryngeal cancer among workers exposed to:

- asbestos
- cutting oil
- wood dust
- grease and oil
- among workers in the paper, metal, leather, food and textile industries
- among barbers, drivers and naphthalene cleaners.

Two years later, Flanders et al (1984) conducted a study in Georgia to identify employment related risk factors for laryngeal cancer. They reported rate ratio estimates above 3.0 for:

- farmers
- textile processors who separated, filtered or dried textile fibres
- labourers and maintenance personnel.

2501199430

The authors commented that "the results of our study ... and the results of other studies suggest that employment in selected occupations is associated with increased laryngeal cancer risk and that the increased risk is not entirely the result of heavier drinking or smoking by workers in these occupations".

Olsen and Sabroe (1984) reported "high risk ratios for laryngeal cancer" for:

- semi-skilled and unskilled workers
- workers exposed to dust
- out-of-doors workers
- drivers
- people working in cement industries and port services.

Genetic Influence

Ramadan et al (1982) noted that "the genetic factor may have some influence on regional and international variation of mortality and incidence rates for cancer of the larynx.

Austin (1982), in his review of the larynx, said that "a possible genetic mechanism of susceptibility to smoking is through the inducibility of the enzyme aryl hydrocarbon hydroxylase (AHH)". Austin continued "it is believed that the chief carcinogens of tobacco smoke are metabolically activated in the cell by AHH, which is subject to genetic control. In the general population, there appear to be three subgroups, low, intermediate and high, for levels of AHH inducibility, corresponding to the homozygous (low), heterozygous, and homozygous (high) gene states (Kellermann et al, 1973). In 1978, Brandenburg and Kellermann reported that patients with laryngeal cancer were more likely to have intermediate and high AHH inducibility than controls".

More recently, Andreasson et al (1987) reported a study in Sweden. They divided the patients with laryngeal cancer into three groups according to their AHH levels and then compared the results with "healthy control material" also divided into three groups. The authors reported "a highly significant overrepresentation of patients with a high AHH level ($p < 0.0005$) as well as a significant underrepresentation of low AHH levels ($p < 0.025$) were found. Smokers with a high AHH level run a fourfold risk of developing laryngeal cancer as compared to non-smokers with low AHH levels. They also develop cancer earlier in life and get recurrences and secondary malignancies more frequently. As in oral and oropharyngeal cancer a high AHH inducibility seems to be of pathogenetic as well as prognostic importance even in laryngeal cancer".

2501199431

Miscellaneous Factors

Tucker (1935) and Hammond (1942) considered that "vocal abuse" appeared to be a predisposing factor or contributing cause in cancer of the larynx. Wynder, Bross and Day (1956) found that edentia (i.e. having no teeth) was more prevalent among larynx cancer patients than among the controls, and that hoarseness and chronic cough were related to cancer of the larynx.

Blunheim (1957) said that exposure to strong heat at work was a factor. Sarma (1958) reported a close association between the incidence of cancer of the larynx and the Assamese type of betel-nut-chewing habit.

Henderson et al (1976) reported a case-control study of nasopharyngeal cancer in several racial groups in California. They reported that "prior history of disease of the ear, nose and throat, occupational exposure to fumes and chemicals, and prolonged exposure to smoke, foreign birthplace and family history of cancer, particularly of the respiratory tract and breast" were associated with the risk of nasopharyngeal cancer. They also suggested "a genetic variation in susceptibility" amongst the Chinese patients studied.
Lin et al (1979) reported a retrospective study of nasopharyngeal carcinoma in Taiwan. They reported that "working under poor ventilation, use of nasal balms or oil for nasal or throat troubles, use of herbal drugs, and anti-EBV antibody titre were found statistically associated" with nasopharyngeal carcinoma. [NB: The last named factor is a measure of the amount of EBV present in the subjects).

7. RECENT REVIEWS ON CANCERS OF THE LARYNX AND PHARYNX

Royal College of Physicians (1977)

The 1977 Report of the Royal College of Physicians commented as follows:

"Cancer of the mouth and throat and oesophagus are all associated with smoking. The risks of smokers getting these forms of cancer are estimated in the main prospective studies as being some 5 to 10 times greater than the risk of non-smokers. This increase of risk is as great for pipe and cigar as for cigarette smokers (US Public Health Service, 1971) and the risk is also raised by heavy consumption of alcohol (Schottenfeld, Gantt and Wynder, 1974; Schwartz et al, 1966). These complicating factors make it difficult to interpret mortality trends over the past half century when pipe smoking has been replaced by cigarette smoking and drinking habits have changed considerably. Death-rates from these forms of cancer have been decreasing over the past 50 years while lung cancer has been increasing rapidly. There were too few deaths from these cancers in doctors to see whether the downward trend of these cancers was steeper than that in all other men over the period 1954 to 1971 (Doll and Peto, 1976). We cannot therefore be sure how far smoking contributes to their causation. These are not very common forms of cancer. In 1973 1,241 men and 653 women between the ages of 30 and 64 in England and Wales died from them, representing 5 and 3 per cent respectively of all deaths due to cancer, and 1.5 per cent and 1.3 per cent respectively of deaths from all causes in the two sexes of these ages (OPCS, 1975). Cancers of the mouth and throat are among those with the highest cure-rates of all cancers so that deaths attributed to them are an underestimate of the real incidence of what may be very distressing conditions. Thus, in the USA in 1967, it was estimated that 20,000 cases of mouth cancer were diagnosed, but only 6,718 deaths from this

disease were recorded (US Public Health Service, 1971). Although we cannot be sure how much tobacco smoking contributes to these conditions, it would be surprising if frequent exposure of the tissues of the mouth and throat to cancer-producing substances did not increase the incidence of cancer there. In several studies it has been found that smokers who stop smoking after treatment of mouth or throat cancers are less likely to have recurrences than those who continue to smoke after treatment (Moore, 1971; Silverman and Griffith, 1972)".

Royal College of Physicians (1983)

The Committee responsible for the 1983 Report of the Royal College of Physicians stated that "we have been careful not to repeat at length points which have become generally accepted". However, they stated "cancers of the mouth, larynx and oesophagus have all been shown to be associated with smoking and here the risks are as great for pipe and cigar smokers as for those who use cigarettes only. They are, however, less common cancers, and fortunately those in the mouth and larynx are often curable".

United States Surgeon General (1971-1979)

Although the Surgeon General (SG) published reports on smoking in 1972, 1973, 1974 and 1975, they mainly re-stated the conclusions of the review prepared in 1971 (see page 8 of this document).

The fifteenth anniversary report (US Department of Health, Education and Welfare, 1979) stated that new evidence has accumulated since 1964 with respect to the relationship between tobacco use and cancer of the larynx and oral cavity. The SG said that "in the case of laryngeal cancer, the accumulated evidence since 1964 has strengthened, but not materially changed, the conclusions of the 1964 Report. In the case of cancer of the oral cavity, the 1964 Report had to base its conclusions primarily on retrospective studies because of the diversity of sites, their varying incidence of tobacco exposure, and the relatively small numbers derivable in the early years of the prospective studies. These studies, unfortunately, varied in approach and either did not separate the several sites of the oral cavity or found the classes of smoking too numerous for testing their significance. Thus, the only firm judgment which could then be made was that a causal relationship exists between pipe smoking and cancer of the lip".

The conclusions of the 1979 Report were as follows:

2501199433

"Cancer of the Larynx

Cigarette smoking is a significant causative factor in the development of cancer of the larynx in men and women and is directly related to several measures of dosage.

Pipe and cigar smokers experience approximately the same risk as cigarette smokers for cancer of the larynx.

There appears to be a synergistic effect between smoking and alcohol intake, as well as between asbestos exposure and smoking, for laryngeal cancer.

There is a substantial decrease in the risk of developing cancer of the larynx with long-term use of filter cigarettes compared to the use of nonfilter cigarettes; ex-smokers, after 10 years of cessation, have mortality rates which approximate those of nonsmokers.

Oral Cancer

Epidemiological studies indicate that smoking is a significant causal factor in the development of oral cancer. The risk increases with the number of cigarettes smoked per day.

Pipe and cigar smokers experience almost the same high risk for oral cancer as experienced by cigarette smokers.

A synergism exists between smoking and alcohol consumption for oral cancer."

United States Surgeon General (1982)

The 1982 Report of the SG (US Department of Health and Human Services) concluded that:

"Laryngeal Cancer

Cigarette smoking is the major cause of laryngeal cancer in the United States. Cigar and pipe smokers experience a risk for laryngeal cancer similar to that of a cigarette smoker.

The risk of developing laryngeal cancer increases with increased exposure as measured by the number of cigarettes smoked daily as well as other dose measurements. Heavy smokers have laryngeal cancer mortality risks 20 to 30 times greater than nonsmokers.

Cessation of smoking reduces the risk of laryngeal cancer mortality compared to that of the continuing smoker. The longer a former smoker is off cigarettes the lower the risk.

Smokers who use filtered lower tar cigarettes have lower laryngeal cancer risks than those who use unfiltered higher tar cigarettes.

The use of alcohol in combination with cigarette smoking appears to act synergistically to greatly increase the risk of cancer of the larynx.

2501199434

Oral Cancer

Cigarette smoking is a major cause of cancers of the oral cavity in the United States. Individuals who smoke pipes or cigars experience a risk for oral cancer similar to that of the cigarette smoker.

Mortality ratios for oral cancer increase with the number of cigarettes smoked daily and diminish with cessation of smoking.

Cigarette smoking and alcohol use act synergistically to increase the risk of oral cavity cancers.

Long term use of snuff appears to be a factor in the development of cancers of the oral cavity, particularly cancers of the cheek and gum."

United States Surgeon General (1989)

The 1989 Surgeon General's Report (US Department of Health and Human Services) stated that "the 1964 Surgeon General's Report concluded that cigarette smoking was causally related to laryngeal cancer in men and that pipe smoking was causally related to lip cancer (US PHS 1964). Subsequent reports reviewed the accumulated epidemiologic evidence that established that cancers of the larynx, oral cavity, and esophagus are caused by smoking in both men and women. The mortality ratios for these cancers are similar for smokers whether they smoke cigars, pipes or cigarettes. A strong dose-response relationship exists, and the risk decreases with cessation, compared with continued smoking. Recent studies have confirmed these findings (Blot et al, 1988; Elwood et al, 1984; Schottenfeld, 1984). Alcohol consumption is also a risk factor for oral, pharyngeal, laryngeal, and esophageal cancer. The combination of alcohol and smoking produces a synergistic increase in risk. In one study (Schottenfeld, 1984), for all upper airway cancers combined, the risk was 8.6 for those smoking 30 or more cigarettes per day in combination with 20 oz. of alchol consumed per week".

World Health Organization

The World Health Organization (1986) concluded that "for cancers of the upper respiratory and upper digestive tracts, all the studies that examined the role of smoking in the absence of alcohol drinking showed an effect of tobacco smoking and a dose-response relationship .... The relative risks observed for cancer of the oesophagus, however, were lower than those for oral and laryngeal cancer. The available data did not allow a firm conclusion to be reached about the relation of pharyngeal cancer to smoking".

2501199435

Ramadan et al (1982)

Ramadan et al (1982) reviewed "the epidemiology of squamous carcinoma of the larynx in England and Wales over the past 70 years". The authors concluded that "there has been a pronounced change in the mortality rates for laryngeal cancer in England and Wales from 1911-1978. This has consisted of an initial sharp rise followed in the 1930s by a steady decline in the mortality for men. The mortality for women began to fall in the late 1940s and has started to rise again over the past 10 years. The M : F ratio has varied surprisingly little over the years, showing a male predominance of about 4 : 1. Urbanization has generally been associated with a higher risk of death from laryngeal

cancer, and mortality has been greatest in manual workers. There is conflicting evidence regarding the role of tobacco smoke in the development of laryngeal cancer, but in England and Wales the time trends in mortality rates follow changes in alcohol consumption rather than tobacco consumption. Much of the available evidence implicates alcohol as having a major role in the pathogenesis of laryngeal cancer."

Austin (1982)

Austin concluded from his review that "most cases of laryngeal cancer could be prevented by eliminating smoking. The control of excess alcohol consumption would eliminate another significant portion. Reduced exposure to asbestos and other occupational carcinogens is within the scope of existing technology, providing that the carcinogen is identified. Therefore, as a preventive strategy, the systematic monitoring for cancer among persons employed in different occupations is needed. Without effective preventive measures, society must rely only upon the early diagnosis and treatment of laryngeal cancer".

8. CONCLUSIONS

1. It would appear that a case of laryngitis was attributed to smoking in 1867 and, some fifty years later, it was claimed that tobacco can cause throat cancer. In the 1930s it was stated that tobacco smoking was an etiological factor in cancer of the larynx although it was also said that there was no conclusive evidence that tobacco was injurious to the throat. Alcohol was first implicated as a factor in laryngeal cancer in 1936 and has been emphasised in many papers since then.

2. In the 1940s and 1950s papers appeared which said that smoking was not a significant factor, or that it had not been proved that smoking played a part, in cancer of the larynx. However, the major epidemiological studies conducted in the 1950s and 1960s alleged that cigarette smoking was a risk factor and that a dose-response effect was evident.

3. The first report on smoking by the Royal College of Physicians (RCP) published in 1962 did not refer to cancers of the mouth, larynx or pharynx, although the first United States Surgeon General's Report, in 1964, said that cigarette smoking was a significant factor in laryngeal cancer.

4. The major epidemiological studies have alleged that cigarette smokers have between about 3 and about 10, or more, times the risk of developing cancer of the larynx than non-smokers. Similar results have been alleged for cancer of the pharynx. Some epidemiological information has alleged that ex-smokers have a lower risk of laryngeal/pharyngeal cancers than current smokers.

5. A range of dietary and occupational factors have been implicated with cancers of the larynx and pharynx, a genetic influence has been suggested and numerous miscellaneous factors have been identified. The most frequently mentioned factor would seem to be alcohol.

6. The latest view of the RCP is that these cancers have been shown to be associated with smoking. The Surgeon General goes one stage further, stating that cancers of the larynx and oral cavity are caused by smoking. The WHO states that there is an effect of tobacco smoking and a dose-response relationship.

APPENDIX 1

DETAILS OF DISEASES OF THE THROAT

EXTRACTS FROM

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32.18 *Diseases of the ear, nose and throat*

DISEASES OF THE NASOPHARYNX

Adenoids

Adenoids is the term used for the nasopharyngeal tonsils, when they become hypertrophied.

CLINICAL FEATURES

Some degree of enlargement of the nasopharyngeal tonsils is normal before puberty and if small, adenoids give rise to no symptoms. When larger, they lead to nasal obstruction either by their size or by producing a chronic rhinitis. As a result of the obstruction, there is mouth breathing, snoring and a toneless voice and in marked cases an 'adenoid facies'. This is recognized by the narrow pinched nares often with mucoid nasal discharge, a high arched palate with crowded teeth, mouth breathing and often a vacant expression. There is doubt as to whether the maldevelopment of the upper jaw is due to adenoids, but the adenoid facies is very characteristic. The nasal obstruction frequently causes sinusitis when the discharge becomes purulent.

A further effect of adenoids is on the function of the auditory tube, causing indrawing of the drums and

deafness which may be persistent or intermittent. Fluid may collect in the middle ear and recurring attacks of otitis media with or without otorrhoea are common.

DIAGNOSIS

Adenoids are best diagnosed by posterior rhinoscopy which can often be performed in quite young children. Often, however, the diagnosis has to be made from the other clinical findings, particularly where there is hypertrophy of the palatine tonsils. A lateral radiograph of the nasopharynx may indicate the pressure of adenoids and sometimes it is necessary to palpate the nasopharynx under general anaesthesia before a definite diagnosis can be made.

TREATMENT

In general, where adenoids are the cause of persistent symptoms, they should be removed with a curette. This is done under general anaesthesia, frequently in combination with tonsillectomy. Care should be taken in recommending this operation where there is any deficiency of the palate, e.g. after cleft palate operations or in a congenitally short palate where removal of the adenoids may lead to inadequate closure of the nasopharyngeal isthmus.

Tumours of the nasopharynx

BENIGN TUMOURS

The commonest benign tumour is an angiofibroma, occurring in boys between 10 and 25 years of age. The tumour grows from the region of the base of the sphenoid, or from the lateral or anterior wall of the nasopharynx. It is basically a haemangioma but there is a variable and often abundant intervascular stroma of fibroblastic fibrous tissue. As the patient grows older the vessels regress and the lesion resembles a simple fibroma. The tumour is of rubbery consistence, and fills the nasopharynx, leading to nasal obstruction; its angiomatous nature may cause severe epistaxis. Although benign, it may expand the face and extend into the orbits, or it may grow into the orifices in the base of the skull, or even erode into the cranial cavity. Deafness may follow blocking of the auditory tube. The tumour occasionally regresses spontaneously in adult life.

Active treatment is by radiotherapy which reduces the vascularity, followed by radical excision, using a transpalatal approach.

MALIGNANT TUMOURS

Malignant tumours of the nasopharynx are usually carcinomata of various types or sarcomata of lymphoid or reticuloendothelial tissue.

Carcinoma

These may be well differentiated squamous neoplasms, but more commonly show a transitional type of epithelium. Differentiation is often poor, and not uncommonly the lesion consists of masses of anaplastic cells very similar to those of a reticulum cell sarcoma. Some tumours, called lymphoepitheliomata, show an intimate mixture of malignant epithelial cells and lymphocytes or lymphoid tissue, and it may be difficult to be sure of the basically carcinomatous nature of the lesion.

Reticuloendothelial neoplasms

Lymphosarcoma and reticulum-cell sarcoma are relatively common in this situation, presumably because of the large amount of lymphoid tissue in the nasopharynx. In addition a soft tissue plasmocytoma is sometimes found; this is histologically similar to the more common plasma cell myeloma of bone marrow (chap. 21) and the patient may eventually develop signs of the disseminated disease. Amyloid deposits are frequently found in this tumour.

Pleomorphic adenoma (mixed tumour)

This tumour is similar to that arising in the salivary glands (p. 19.14), but is usually more aggressive, and tends to recur more consistently. It should therefore usually be regarded as a malignant lesion.

These tumours commonly arise on the lateral wall of the nasopharynx. They present clinically in four ways, (1) nasal obstruction, (2) metastatic deposits in the cervical lymph nodes, especially in the case of carcinoma, (3) involvement of the auditory tube causing deafness and (4) invasion of the base of the skull leading to cranial nerve lesions. Diagnosis is by posterior rhinoscopy, radiographs of the base of the skull, and palpation and inspection of the nasopharynx under general anaesthesia; biopsy is necessary for accurate diagnosis. Treatment is by radiotherapy.

Infection and ulceration of the pharynx

Infection of the pharynx is described on p. 12.18 and other diseases on p. 19.8. Patients are referred to an ENT specialist when there are problems of diagnosis or when complications requiring surgical treatment occur.

In the diagnosis of throat conditions, it is important to examine the nose, nasopharynx and accessory sinuses as well as, in some cases, the larynx and lower respiratory tract. The examination should also include palpation of the cervical lymph nodes and in many cases other superficial lymph nodes. A full blood examination, serological tests and a throat swab are essential. When malignant disease is suspected, biopsy is required; if one tonsil is enlarged without ulceration, tonsillectomy is preferable to a local biopsy. Where an enlarged node in the neck is thought to be malignant, it is important to exclude a

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primary tumour in the upper respiratory and gastro-intestinal tracts before biopsy of the gland is performed.

TONSILLECTOMY

The indications for this operation are recurrent attacks of tonsillitis and persistent tonsillilar infections or cervical adenitis. Enlargement of the tonsils is not an indication for operation unless gross hypertrophy causes choking as soon as the child falls asleep or has difficulty in swallowing. These symptoms are rapidly cured by tonsillectomy. Occasionally patients are referred for tonsillectomy because of recurring upper respiratory tract infections, rheumatism, glomerulonephritis or psoriasis. The tonsils should be removed in these cases only if there is obvious evidence of chronic infection, e.g. redness of the pillars of the fauces, purulent secretion in the crypts or cervical adenitis, not responding to conservative measures.

Contraindications to tonsillectomy are (1) an acute upper respiratory tract infection, (2) an epidemic of poliomyelitis and (3) a history of a bleeding tendency; in the latter case the morbidity caused by recurring infection may justify tonsillectomy after a full haematological examination, provided arrangements for immedate blood transfusion are available.

Type of operation

In adults, tonsils are removed by dissection under general anaesthesia; this permits ligature of the vessels after the tonsils have been removed. The same operation may be done in children, but many doctors favour a guillotine type operation because it can be done more quickly and the postoperative recovery is quick.

Complication of tonsillectomy

The most common and important complication is reactionary haemorrhage within a few hours of operation and it occurs as often after dissection as after the guillotine operation. It may be due to a blood clot in the tonsillar bed not allowing contraction of the vessels. If bleeding does not stop after removal of the clot, no time should be lost in returning the patient to the theatre for ligature of the bleeding point under general anaesthesia. Blood transfusion should be started at the same time, if there is evidence of shock.

Secondary infection is less common and occurs 5–7 days after operation, caused by sloughing of the tonsil bed. It almost invariably responds to rest in bed with antibiotics and sedation. Secondary haemorrhage may be controlled by stitching of the faucial pillars.

Other rare complications are aspiration of blood or a tooth leading to lung collapse or a lung abscess, otitis media and acute torticollis. Earache is present at some stage after every tonsillectomy and may be due to referred pain, but the tympanic membrane should be inspected in every case.

PERITONSILLAR ABSCESS (quinsy)

Peritonsillar cellulitis without pus formation may resolve with antibiotics. Once an abscess has formed, it must be opened. This is done without anaesthesia either by passing a pair of curved forceps through the intratonsillar fossa or by inserting St Clair Thomson forceps directly through the anterior pillar. When the forceps have entered the abscess, the points are separated to widen the opening into the abscess. The opening of a quinsy is momentarily painful, but the subsequent relief is dramatic. The tonsils should be removed when the infection has subsided, as otherwise a recurrence of the quinsy is likely.

DISEASES OF THE LARYNX

Much the most important and common symptom is interference with phonation. This usually takes the form of hoarseness but there may be complete loss of voice. Obstruction of the airway causes dyspnoea, stridor or asphyxia. Cough, haemoptysis and dysphagia are less common symptoms. Pain occurs in deep ulcerative lesion and is referred to the ears; in superficial infections the patient may complain of a raw feeling in the throat.

Methods of examination

This is carried out by indirect laryngoscopy. A large mirror of about 24 mm in diameter is warmed enough to avoid misting. The patient then opens his mouth wide and protrudes the tongue as far as he is able. The tongue is retained in this position by holding it in the left hand with a swab. With illumination from a bull's eye lamp and a forehead mirror, the warmed mirror is passed through the mouth and placed against the soft palate (fig. 32.8). The patient is instructed to breath regularly through the mouth. It is now possible to see the epiglottis, and the posterior part of the inlet of the larynx through the mirror. The patient now says 'ee'; this raises the whole larynx and tilts it forwards allowing inspection of the whole of the interior of the larynx. As the patient breathes in and out, the movements during respiration can be observed, and when he says 'ee' the movements of phonation are seen. It is only by indirect laryngoscopy that the movements of the cords can be demonstrated. This is important in the diagnosis of laryngeal paralysis and in assessing the invasiveness of a tumour. The view obtained by indirect laryngoscopy is a mirror image and, in description, it is important to correct for this (fig. 32.9).

In most cases indirect laryngoscopy can be carried out without anaesthesia, but occasionally spraying of the throat with 10 per cent cocaine is required. It is important

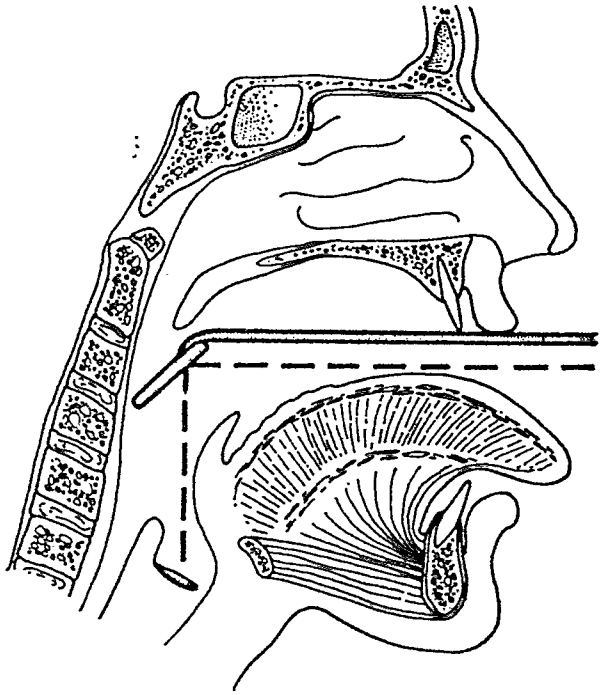

FIG. 32.8. Indirect laryngoscopy.

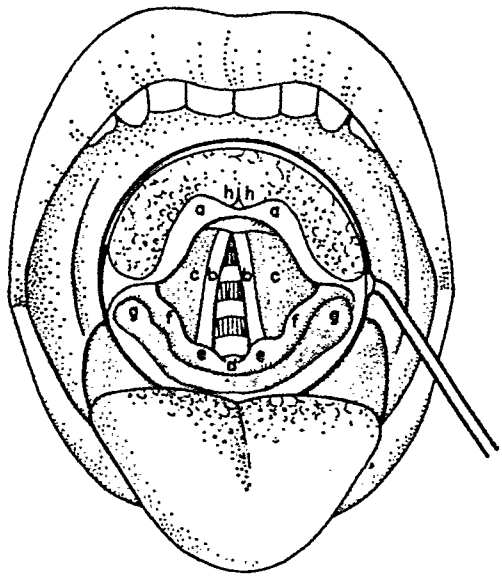

FIG. 32.9. Features of the larynx seen by indirect laryngoscopy. (a) Epiglottis, (b) vocal cord, (c) vestibular cord (false cord), (d) interarytenoid region, (e) corniculate cartilage, (f) cuneiform cartilage, (g) pyriform fossa, (h) vallecula.

that the cocaine should not be swallowed, but spat out into a basin, to avoid absorption of an excessive amount.

If it is not possible to obtain an adequate view of the larynx with the mirror, or if a more detailed inspection is required or if a biopsy is to be performed, direct laryngoscopy, usually under general anaesthesia, is carried out. If malignant disease is suspected, the neck is examined for enlarged lymph nodes, and the larynx palpated for broadening and to exclude fixation to surrounding structures. Other methods of investigation are soft tissue radiography, tomography and contrast radiography.

Acute epiglottitis

Acute epiglottitis is a very dangerous infection of the epiglottis by *H. influenzae* in very young children. The epiglottis may be seen as a bright red cherry-like swelling and it can kill by asphyxia within a few hours. It should be treated with ampicillin; the patient must be closely observed and tracheostomy performed if necessary.

Acute laryngitis

Acute laryngitis is a common complication of acute upper respiratory infections such as coryza, influenza, tonsillitis, sinusitis, etc. It is particularly liable to occur with excessive use of the voice during such infections.

Hoarseness is the main symptom and may vary from slight roughness of the voice to almost complete aphonia. Rawness of the throat may progress to actual pain which is worse on coughing. Swallowing may be painful. The degree of systemic upset depends on the causative condition.

In infancy it often occurs as part of the laryngotracheo bronchitis caused by respiratory syncytial viruses.

On examination, there is diffuse redness of the whole larynx and sticky secretion may be retained on the mucosal surfaces. There may be diffuse swelling of the vocal cords, and slight muscle paresis with bowing of the vocal cords on phonation may be observed. The narrow airway of babies is more easily obstructed and they must be carefully watched for signs such as cyanosis, increasing restlessness, rising pitch of the stridor and costal recession. The patient should be kept in his room and at an even temperature. If there is pyrexia, he should be in bed. Treatment consists of resting the voice. Steam inhalations with menthol are helpful, but critically ill babies are usually nursed in a small clear plastic tent and a mist of water vapour. The causative condition should receive appropriate treatment.

Acute laryngeal stridor

When babies learn to handle and transfer objects to the mouth, acute stridor may result from the inhalation of a foreign body.

Oedema of the glottis

Acute oedema of the larynx most commonly results from infection in the pharynx, e.g. quinsy, or in the neck, e.g. Ludwig's angina. It may also result from (1) trauma, such as a direct injury to the larynx, (2) a scald as when a child drinks a hot fluid, (3) carcinoma of the larynx, (4)

reaction to radiotherapy, (5) perichondritis due to carcinoma, radiotherapy or rarely tuberculosis or syphilis, (6) hypersensitivity states, e.g. angioneurotic oedema, (7) as part of a generalized oedema, e.g. in glomerulonephritis or heart failure and (8) intrathoracic swellings which obstruct the venous return from the head and neck.

The oedema is mainly confined to the free edge of the epiglottis, aryepiglottic folds and arytenoids, i.e. the laryngeal inlet; the vestibular folds are also involved but the cords and other parts escape. The mucosa is pale in non-inflammatory oedema and red in inflammatory lesions.

TREATMENT

Rest in the upright position in bed is essential. The atmosphere should be humidified by a steam kettle. Ice to suck or cocaine and adrenaline sprays may reduce the oedema. Antihistamines and adrenaline, 0·5–1 ml 1 : 1000 solution by subcutaneous injection, are given in angio-oedema (p. 31.28). The causative condition should be treated. If an adequate airway cannot be maintained by these measures, tracheostomy is required.

Chronic laryngitis

As in acute laryngitis, chronic laryngitis results from excessive use of the voice, particularly in the presence of infection of the teeth, tonsils or sinuses, exposure to atmospheres containing excessive dust, fumes, humidity or dryness, and excessive smoking. It is a frequent accompaniment of chronic bronchitis.

Hoarseness is the main symptom and is often worse in the morning. There may be a constant desire to clear the throat and this irritable cough may produce pellets of mucus.

On laryngoscopy there is redness, most marked on the vocal cords and vestibular folds, and oedema may develop. The cords and false cords frequently hypertrophy and the swelling is usually smooth and regular, but occasionally nodular, when it may be difficult to distinguish the appearances from a carcinoma.

TREATMENT

At first, voice rest and the use of oil of pine steam inhalation should be combined with eradication of any sepsis.

Once the voice has improved, overuse of the voice should be avoided and speech therapy may be required to correct faulty voice production. Bad atmospheric working conditions should be avoided. In resistant cases it may be necessary to strip oedematous portions of mucosa under direct laryngoscopy. It cannot be emphasized too strongly that no case of hoarseness should be treated as laryngitis for longer than three weeks without an adequate inspection of the vocal cords. An early carcinoma of the vocal cord, where the prognosis is good, may be missed in this way and the opportunity of treatment with good prognosis lost.

Tuberculous laryngitis

This was once a common complication of pulmonary tuberculosis, but rarely occurs in patients treated with antibiotics. It may also occur in acute miliary tuberculosis and as a sequela of lupus of the face, nose and pharynx. The voice is weak and hollow, and there may be pain on speaking or swallowing fluids. Laryngoscopy may show characteristic infiltration of the arytenoids and tuberculous ulcers of the vocal cords.

In any chronic case of laryngitis, it is important to suspect the possibility of tuberculosis and to examine the sputum and radiographs of the chest. Sometimes a biopsy is required.

Syphilitic laryngitis

Syphilitic infection of the larynx is now rare in Britain. Formerly laryngitis was common in the untreated secondary stage and also occurred in congenital infection and the tertiary stage of acquired disease. Gummata may be difficult to distinguish from malignant disease and biopsy may be required in addition to serological tests for syphilis (p. 13.7).

Laryngeal polyp

A polyp, usually seen at the junction of the anterior and middle thirds of one vocal cord, may result from organization of a small haematoma, due to voice strain, often during a laryngeal infection. It causes hoarseness. In early cases resolution may occur with voice rest, but once there is organization, removal under direct laryngoscopy is required.

Vocal nodules

These are called singer's nodes because they are seen in singers, particularly sopranos and tenors, but they also occur in others who use their voices excessively, with faulty voice production. Initially the voice loses its quality and later becomes hoarse. On examination, a white smooth elevation is seen at the junction of the anterior and middle thirds of one or both vocal cords. When very small, resolution may occur with prolonged voice rest, but in most cases surgical removal is required. This should be done under direct laryngoscopy using an operating microscope so that the removal can be precise, avoiding damage to normal structures. Aftercare is important, and voice abuse should be avoided; speech therapy or retraining of the singing voice may be necessary.

Keratosis of the larynx

In keratosis or leucoplakia, white raised patches occur on the vocal cords. It has been suggested that the

condition is commonest in those subject to recurring laryngitis, and it is important because in some cases it is premalignant.

The main symptom is hoarseness and, on examining the larynx, the white patches are seen. Biopsy is needed to confirm the diagnosis and to exclude malignancy. The patient should be kept under prolonged supervision and, if there is a change in the voice or extension of the lesions, a further biopsy is required.

Laryngeal paralysis

AETIOLOGY

All the muscles of the larynx are supplied by the recurrent laryngeal nerve with the exception of the cricothyroid muscle; this is supplied by the external laryngeal nerve, a branch of the vagus. Laryngeal paralysis may result from lesions involving the vagus in the medulla, e.g. vascular lesions, syringomyelia, tumours, motor neurone disease and poliomyelitis. The vagus nerve may also be involved as it passes to the jugular foramen, e.g. by an acoustic neuroma, carcinoma of the nasopharynx, basal meningitis or fracture of the base of the skull. High in the neck, the vagus nerve may be damaged by trauma or by involvement in inflammatory or malignant disease, particularly of lymph nodes. The left recurrent laryngeal nerve passes further down into the superior mediastinum than the right and is particularly likely to be involved in carcinoma of the lung or a mediastinal metastasis from such a tumour. Other causes of paralysis in the mediastinum are, on the left side, aneurysm of the aorta, carcinoma of the thoracic oesophagus, mediastinal masses, e.g. lymphosarcoma, lymphadenoma or secondary breast tumour, and tuberculosis of the cervical pleura; and on the right side, aneurysm of the subclavian or innominate arteries, carcinoma of the apex of the right lung, tuberculosis of cervical pleura. In the neck the recurrent laryngeal nerves are liable to damage as they pass in the groove between the trachea and oseophagus from diseases of or surgery to the thyroid gland, carcinoma of the cervical oesophagus and from malignant disease involving cervical lymph nodes.

CLINICAL FEATURES

Semon's Law states that in incomplete paralysis of the vocal cord, the function of the adductor muscles only is retained and the cord lies adducted to the midline position. In complete paralysis, the cord lies midway between full abduction and adduction as it does after death. From this the effect of paralysis can be predicted.

In unilateral incomplete paralysis, e.g. after trauma during thyroidectomy, the affected cord lies in the midline. There may be very transient hoarseness, but often the voice is normal because the normal cord can adduct to the fixed cord in phonation. It can also abduct sufficiently to give a good airway.

In unilateral complete paralysis as in carcinoma of the lung, the affected cord is in the cadaveric position. The normal cord does not meet the affected cord on phonation and only a whisper with a great deal of air escape is possible. A normal explosive cough is not possible and a cough is ineffective. The airway is quite free. If the patient survives long enough, the normal cord compensates by moving across the midline to meet the affected cord with improvement in the voice. In bilateral incomplete paralysis, e.g. after thyroid surgery, both vocal cords are adducted to or near to the midline. This interferes with respiration and tracheostomy may be required. In other cases respiratory embarrassment may only occur on moderate exertion. The voice is good and strong; if a tracheostomy is done a flap valve allows inspiration through the tube and expiration through the cords. If improvement does not occur after 6 months, an operation may be done to displace the more affected cord laterally. This improves the airway at the expense of the strength of the voice, but this may be accepted by a young woman so that she can dispense with a tracheostomy.

In bilateral complete paralysis, e.g. after a brainstem vascular lesion, both vocal cords lie in the cadaveric position. The airway is good but the cough is ineffective and the lower respiratory tract has lost its upper sphincter. Because both vagus nerves or nuclei are affected there is often loss of sensation in the larynx; this aggravates the risk of aspiration of food and saliva. The voice is very poor. The prognosis is usually grave, but in non-progressive lesions, aspiration may be minimized by tube feeding and tracheostomy may also be required.

FUNCTIONAL APHONIA

Unlike organic lesions a functional disorder produces paralysis of the adductors of both vocal cords during phonation. This occurs mainly in young women during emotional stress. The voice may be lost completely or more often reduced to a whisper; the voice is usually lost suddenly and also recovers suddenly. Although the cords fail to adduct on phonation, they do so on coughing. The patient may not speak but she can be heard to cough. On laryngoscopy the cords will be seen to adduct on coughing but not on phonation. The most satisfactory treatment is speech therapy.

Tumours of the larynx

BENIGN TUMOURS

Papillomata occur singly on the vocal cord in adults and give rise to hoarseness; they are removed by direct laryngoscopy. Multiple papillomata occur in infants and small children. They are seen on the cords and vestibular folds but may extend to the epiglottis or to the trachea

and bronchi. The papillomata interfere with phonation and with the airway, and treatment consists of endoscopic removal with care to avoid damaging the underlying structures. This requires to be done repeatedly until puberty when the condition tends to clear up. In some cases tracheostomy is required to maintain the airway.

Chondroma, angioma, lipoma, rhabdo- and leiomyoma and neurofibroma also occur rarely in the larynx.

MALIGNANT TUMOURS

Although adenocarcinoma, basal cell carcinoma and sarcoma occur, most malignant tumours of the larynx are squamous cell carcinomata, ranging from well differentiated highly keratinized tumours to anaplastic tumours.

The commonest site is the anterior half of one vocal cord, i.e. the glottic carcinoma. When a tumour arises in the larynx above the vocal cords it is known as supraglottic, if below the cords, subglottic.

It is fortunate that glottic carcinoma is the commonest type, because, if it is diagnosed early, the prognosis is excellent. Approximately 80 per cent of early glottic cancers are cured by treatment. As the growth is on the free edge of the cord, hoarseness occurs early and may be the only symptom. Persistent hoarseness should never be neglected and labelled 'laryngitis'. If it lasts for more than 3 weeks, the vocal cords should be seen by either indirect or direct laryngoscopy. While a carcinoma of the vocal cord is confined to the anterior half of the cord and does not extend anteriorly to the anterior commissure, posteriorly to the arytenoid or laterally into the muscle, there is little tendency to metastasize to regional lymph nodes. Once it has spread beyond these limits, the deep cervical lymph nodes are usually soon involved. An anterior growth may spread first to the prelaryngeal node overlying the coricothyroid membrane. On indirect laryngoscopy a carcinoma is seen as an irregular thickening of the vocal cord which may appear grey. Tumours in other sites in the larynx may be more papillary or have the appearance of a malignant ulcer. In late cases there may be broadening of the laryngeal skeleton, fixation of the larynx to the prevertebral fascia, or invôlvement of the regional nodes. Distant metastases occur only rarely.

TREATMENT

The usual treatment in all sites is radiotherapy but a few surgeons select some cases for primary surgical excision. If there is a failure to respond to radiotherapy or if there is recurrence of tumour after an initial response, total laryngectomy is usually required. In this operation the whole larynx including the laryngeal cartilages and hyoid bone together with the upper segment of the trachea are excised. The anterior wall of the pharynx is repaired to restore the food channel and the lower cut end of the trachea is brought out into the neck as a terminal tracheostomy. Most of these patients learn to speak using an oesophageal voice, i.e. air is swallowed into the oesophagus and regurgitated to vibrate the pharyngeal sphincter, which replaces the vibrations of the vocal cords.

Swellings in the neck

Swellings in the neck present a common diagnostic problem and are conveniently considered here. They may lie laterally or in the midline.

LATERAL SWELLINGS

Lymph nodes

The cervical lymph nodes may be enlarged in tuberculosis, in the reticuloses, by secondary carcinoma spreading from the lip or tongue, thyroid, pharynx, larynx or lung, and by ascending spread from a breast carcinoma or, on the left side of the neck, from the stomach and pancreas via the thoracic duct.

In tuberculosis the nodes are characteristically matted together; they are firm at first, but soften as they become caseous. Various groups of nodes may be affected in turn; most commonly the upper deep cervical nodes, particularly the tonsillar gland or jugulodigastric node are involved, and by extension the lower deep cervical nodes in relationship to the jugular vein. In previous years many patients developed multiple cervical scars and sinuses, often disfiguring ones, resulting from the drainage of tuberculous abscesses or from radical surgery for the excision of tuberculous nodes and sinuses in the neck. Since tuberculosis is less frequent nowadays, such lesions are rarely seen in Britain (p. 14.9).

Today, the commonest cause of lymph node swelling of the neck in young adult patients in Britain is infectious mononucleosis. Less common is lymphoreticulosis; such nodes have a rubbery feel, are separable into discrete masses and attain a large size painlessly in the short space of a few months. Many of these patients are found to have other masses of enlarged lymph nodes in the chest and abdomen, and splenomegaly.

In enlargement of lymph nodes secondary to malignancy of the upper oesophagus and larynx, bronchus and breast, the affected nodes are usually matted together as one fixed mass and stony hard. The group of nodes involved is usually closely related to the primary neoplasm, but malignant cells may on occasion spare the nearest group to involve one more remote.

The cervical lymph node enlargement from a secondary carcinoma of the thyroid gland may be the presenting feature of this disease; this is not uncommon in the papillary type of thyroid carcinoma, and the lymph node lesion has been known as a lateral aberrant thyroid.

Branchial cyst

This owes its origin to a congenital defect in the formation of the cervical sinus (vol. 1, p. 18.34). It develops when the second branchial arch overgrows to meet the fifth and the cervical sinus formed as a depression exterior to the primitive pharyngeal region, in the floor of which lie the third and fourth arches. This sinus customarily closes, but should it persist it forms a branchial cyst. This potential space does not become apparent clinically until early adult life when the patient, usually a young woman, presents with a swelling in the upper neck at or near the angle of the jaw. The swelling is usually fluctuant and transilluminates; it is initially painless. However, it may become inflamed, tender and painful. The cyst is usually lined partly by squamous epithelium and partly by ciliated columnar epithelium. Characteristically there is abundant lymphoid tissue deep to the epithelium. The cyst is easily excised with lasting cure, provided all the branchial tissue is removed.

Should the second arch fail to fuse with the fifth, an opening remains in the neck, usually related to the anterior border of the sternomastoid. A fistulous track, **a branchial fistula**, leads between the main arches of the neck to the pharynx near the tonsil, which region represents the territory of the second branchial pouch (vol. 1, p. 18.35). Excision is also indicated.

Cystic hygroma

This also presents as a fluctuant swelling in the neck; it is common in children, and occurs in the posterolateral part of the neck, often extending indeed into the suprascapular area (p. 17.35).

Goitre

A goitre may extend into the lateral part of the neck. Asymmetrical nodules of the thyroid gland present in one lobe are usually easily recognized as part of the main thyroid gland. Diffuse enlargement of the thyroid gland is recognized by its characteristic upward and downward movement on swallowing.

Rarer causes

These include aneurysmal dilation of the carotid vessels, with accompanying expansile pulsation, and carotid body tumours which present as firm swellings; they may transmit the carotid pulsation and give an erroneous clinical impression of aneurysm.

MIDLINE SWELLINGS

The commonest midline swelling is an enlarged thyroid or goitre. Rarer causes are dermoid cyst (vol. 2, p. 28.5), effusion into a subhyoid bursa, enlargement of the lymph nodes in the suprasternal space, the appearance at this site of expanding intrathoracic aortic aneurysm, and a thyroglossal cyst.

Thyroglossal cysts arise in the thyroglossal duct, which is the original outgrowth of primitive embryonic thyroid tissue from the thyroid bud posterior to the tuberculum impar at the junction of the anterior and posterior thirds of the embryonic tongue (vol. 1, pp. 18, 30, 34). The duct extends downwards into the neck as a column of cells, and the mature thyroid gland is derived from this. A thyroglossal cyst results from the persistence of this duct, and may arise anywhere in the midline from the posterior third of the tongue in the line of the thyroglossal duct to the pyramidal lobe of the thyroid gland (vol. 1, fig. 18.57). The cyst has an epithelial lining which may be squamous or ciliated columnar, or a mixture of the two, and foci of thyroid glandular tissue may be seen in its wall. Like a branchial cyst, a thyroglossal cyst may become inflamed and the skin over it may break down and form a fistula. The skin at the site of a recent fistula is often puckered. Some thyroglossal cysts extend behind the hyoid bone and the track of the thyroglossal duct may loop up and over it before reaching the base of the tongue. For this reason the cyst, the entire track and the central portion of the hyoid are usually excised in one piece.

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APPENDIX 2

EXTRACTS FROM

LARSON, HAAG AND SILVETTE, 1839-1959

EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

Before 1900

According to the Boston Medical and Surgical Journal (*20:* 112–113, 1839), within less than 20 years of the time of writing, a new disease had developed in the country almost exclusively confined to parish ministers, consisting of loss of tone in the vocal organs attended by a sense of fatigue in the muscular apparatus of the throat, and accompanied by a peculiar dryness and rigidity of the lining membrane of the larynx; all of these circumstances concurred to destroy the original character of the voice, and finally to incapacitate many from discharging their pastoral duties. Dr. Mauran offered the observation that, to his knowledge, those clergymen who used tobacco did not suffer from this condition, from which it was inferred that smoking or chewing kept up a secretion in the neighborhood of the glottis, favorable to the good condition and healthy action of the vocal box. In contrast to the clergy of olden times who smoked and chewed very universally, since the great temperance reformation commenced and tobacco had been anathematized, it was now extremely rare to find any of the newcomers into the ministry who would tolerate tobacco. Not unnaturally, these observations raised a storm of controversy, which follows in chronological order: Woodward (*ibid.*, pp. 172–173) stated that in his experience, quite a large number of those suffering from the condition were users of tobacco, and he implicated instead a modern practice of preaching in vestries and thickly crowded, close and warm rooms, and afterwards inhaling cold air while heated. Mauren (*ibid.*, pp. 203–208) defended his position; and N. H. Allen (*ibid.*, pp. 220–222) agreed in general with Woodward that tobacco was injurious to the voice. R. A. M. (*ibid.*, pp. 247–248) was not able to agree with Woodward as to the pernicious effects of tobacco, since so many use it and apparently enjoy good health. "Senex" (*ibid.*, pp. 248–251) presented cases to show that loss of voice, though more frequent within the last 20 years, was not unknown at a much earlier period, and that in one case, to his knowledge, tobacco was not a preventive. From his personal knowledge, Woodward (*ibid.*, pp. 263–266) listed 3 cases of loss of voice in smokers; and Mauren (*ibid.*, pp. 343–347) cited 3 cases in which the condition was cured either by the assumption or resumption of smoking. Bacon (*ibid.*, pp. 280–283; 402) concluded that the affection was caused by speaking, and the remedy was to cease to speak; in 3 cases of bronchitis in clergymen recently come to his attention, 1 habitually used tobacco, 1 took water while speaking, and 1 did neither. It was reported (*ibid.*, pp. 316–318) that impairment of voice among clergymen was very rare in the South, while the practice of using tobacco was almost universal, and several cases were cited in which cessation of the use of tobacco led to the appearance of severe throat symptoms, which were corrected when the use of tobacco was reestablished.

Regarding the effect of smoking on the voice in ordinary individuals, Wright (1846) remarked: "Particularly have I observed the buccal membrane to become vascular, swollen, irritable, and prone to hemorrhage. I have never observed an exception to the fact that in smokers the voice has deepened in tone (I suppose from relaxation), or become hoarse or oppressed through excessive mucous secretion. Many an irritable nervous cough, without increased secretion from the tracheobronchial membrane, and many a cough dependent upon increased secretion, have I known to follow the frequent use of tobacco in smoking."

EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

Gibb (1863) stated that the fauces, pharynx, larynx, and trachea were much more frequently affected from excessive smoking than were the bronchi and mouth:

Stugocki (1867) described a case of tonsillitis attributed to pipe-smoking.

Stugocki (1867) attributed a case of laryngitis to smoking;

According to Ladreit de Lacharriere (1878), the angina of smokers is characterized by swelling, redness, dryness, and insensibility of the mucous membranes of the soft palate and of the pharynx. The swelling is uniformly distributed; it is particularly appreciable at the uvula, which presents a much larger volume and which is sometimes deviated slightly to either the right or left. The mucous membrane is not red, as in acute phlegmatic conditions, but is of a darker color; it is rather a congestive red than inflammatory. The dryness of the throat seems evident; the epithelium which covers the mucous membrane is glossy and brilliant. The patients show no pain, no sensitiveness, and invariably declare they have no sore throat; they demand care only after the subjective symptoms (buzzing and deafness) appear.

Rumbold (1880) considered that the local effect of tobacco on the mucous membrane of the nose, throat, and ears was predisposing to catarrhal disease through causing a more permanent relaxation and congestion than any known agent; and, in the presence of such changes, even slight exposure to cold results in catarrhal inflammation.

According to Rumbold (1880), the use of tobacco should be immediately discontinued by every catarrhal patient.

A writer who signed himself "M. D." (1885) reported a case of chronic pharyngitis kept up by excessive cigarette-smoking.

Coomes (1887) held that 95% of smokers have something abnormal or unhealthy about the upper air passages—pharyngitis, laryngitis, chronic irritation in the nose.

According to Bosworth (1889), pharyngeal or nasal catarrh should not be attributed to the use of tobacco; according to Mulhall (1895a, b, c), tobacco produces, at most, a slight hyperemia or insignificant catarrh in the healthy throat.

In many cases, an existing catarrhal condition may be aggravated by tobacco (Bosworth, 1889; Mulhall, 1895a, b, c).

Jankau (1894) recommended that smoking be stopped in all diseases of the larynx and pharynx.

C. C. Rice (1897) reported that constant contact of tobacco-smoke with the mucous membrane of the respiratory tract resulted in the development of inflammatory conditions in those disposed to disease of this portion of the body much earlier in life than would otherwise be the case. In his experience, smoking caused advanced atrophic nasal catarrh, with dryness and congestion of the pharynx.

EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

1900 - 1919

Langmaid (1904, 1905, 1943) claimed he could recognize the non-smoker by the appearance of the throat.

Langmaid (1904, 1905, 1943) believed that tobacco-smoking was not only harmful to the throat as a direct irritant, but that it produced vasomotor disturbances of the pharyngeal mucous membrane through its toxic effects upon the nervous system.

In Lack's (1905) experience, corroborated by careful inquiry among a large number of singers and other professional voice-users, the effects of tobacco-smoke on the throat were greatly exaggerated. Lack considered it safe to state that moderate smoking never originated any affection of the throat worthy of the name, causing at most a slight hyperemia of the parts with which the smoke comes in contact, or an insignificant catarrh; the slight huskiness of the voice ascribed to smoking will more often be found to depend upon alcoholism or dyspepsia than upon excessive smoking.

P. Steiner (1906) described 3 cases of cancer of the larynx; one of the patients used tobacco excessively.

After a review of the literature, Reik (1910) stated that there was not one scintilla of evidence that malignant disease of the throat was due in any way to the use of tobacco. Other writers, however, have maintained that tobacco can cause throat cancer (Abbe, 1916a; Lickint, 1930b); and Wynder (1956) considered the evidence as good that tobacco is a causative agent in cancer of the hypopharynx.

In a series of 136 cases of carcinoma of the pharynx, 33 patients designated themselves as heavy and very heavy smokers; 8 chewed tobacco (Schumacher, 1912).

With respect to tuberculosis of the larynx, Dworetzky (1918) stated that local irritants, such as tobacco, have a deleterious effect on the larynx, producing a catarrhal condition with consequent formation of a favorable site for the implantation of the tubercle bacillus; therefore, tobacco was contraindicated in tuberculous lesions of the larynx. Duboff (1918) studied 1,000 case-histories of 793 males, of whom 46.4% were smokers, and of 207 females, none of whom smoked. Among the males, throat tuberculosis was no more common among smokers than among non-smokers; among the females, the incidence of throat tuberculosis was as high as among the males, from which the author concluded that throat complications were no more frequent in tobacco-users than in those who use no tobacco, and that tobacco obviously did not predispose to laryngeal complications. In commenting upon this paper, The Lancet (*1:* 745, 1918) suggested that Duboff's argument was based on rather slender statistical evidence.

EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

1920 - 1929

Kelly (1921) directed attention to an uncommon variety of acute laryngitis characterized by the deposition of fibrin and the occasional formation of erosions of the vocal cords which he encountered in 40 soldiers during World War I; among the many predisposing causes of this condition, he instanced the overuse of tobacco.

Ferbrüggen (1923), who considered the chief irritant in tobacco-smoke to be ammonia, stated that, if a patient with chronic catarrh could not stop smoking, one should recommend to him the cigarette, which produces less ammonia than the cigar, to be used in moderation without inhaling. Mentholated cigarettes were especially recommended.

W. M. Johnson (1929) stated that most inveterate smokers show some congestion of the pharynx, regardless of the brand of tobacco smoked;

, W. M. Johnson (1929) was convinced, as a result of more than 3 years' clinical study, that the chief effect of tobacco-smoking was a local one exerted on the mucous membrane of the pharynx, less frequently on the larynx and trachea, and exceptionally on the bronchi.

Bogen (1929) found that 5% of smokers studied by him complained of hoarseness:

In Bogen's (1929) series of smokers, 30% reported coughing.

Of 33 cases of cancer of the fauces in his series, 32 (including 1 woman) were heavy pipe-smokers; and so constant was the association of prolonged smoking with this condition that Mowat (1929) was tempted to call it *the* "smoker's cancer."

EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

1930 - 1939

Some writers have expressed the belief that tobacco-smoking is an etiological factor in the development of cancer of the larynx (Lickint, 1930b; Jackson and Jackson, 1939, 1941; Heermann, 1941; Wynder, 1952b, 1956; Wallner, 1954b: Blümlein, 1955, 1957).

F. L. Hoffman (1931) stated that cancer of the larynx had increased from 0.5 per 100,000 cancer deaths in 1915 to 0.9 in 1923, concomitant with an enormous increase in cigarette-smoking. But Orton, (1938) stated that no great increase of cancer of the larynx has followed promiscuous smoking of cigarettes by either men or women.

Hoffman (1931) reported that 13 of 26 patients with cancer of the tonsils were heavy smokers.

(of cancer of the larynx)

F. L. Hoffman (1931) reported 37 cases, of whom 16 were heavy smokers; G. Tucker (1935), 200 cases, of whom 25 gave a history of excessive tobacco-use; Orton (1938), 102 cases, of whom 38 gave a history of excessive tobacco-use; Heermann (1941), 30 cases, of whom 26 were habitual heavy smokers; A. E. Hammond (1942), 15 cases, of whom 6 gave a history of excessive smoking.

Felderman (1931) also stated there was no conclusive evidence that tobacco was injurious to the throat, and added: "Not only is smoking a social habit but it is a substantial help to those who follow the profession of speaking or singing, for in both of these undertakings a certain amount of mental labor and concentration is required, whether in composing speeches or studying an operetta. Smoking is a much safer habit than over indulgence in foods."

Moratti (1932) pointed out that case-histories of patients with leukoplasia, epithelioma of the mouth, carcinoma of the hypopharynx, esophagus, and stomach, almost always reveal an inveterate habit of smoking and chewing tobacco.

H. Farrell (1933) examined the nose, throat, and chests of 85 men and 15 women cigarette-smokers, and reported that "though slight, there may be seen and felt some changes of an inflammatory nature in the different tissues of the gums, buccal surface, tongue, tonsils, pharynx, larynx, trachea, and esophagus of the inveterate cigarette-smoker. However, this chronic catarrhal condition of the mucous membrane is seldom, if ever, provoking, and it is a rare occasion that the habitue calls on a specialist for relief of sore throat."

Pipe-smoke and cigar-smoke are not inhaled because of their harshness, and these, according to Thys (1935), lead to cancer of the buccal cavity; while, because it is less irritating, cigarette-smoke is deeply inhaled, and hence leads to pulmonary cancer in heavy cigarette-smokers.

G. Tucker (1935) considered that excessive use of tobacco was probably a predisposing cause of a number of his cases of cancer of the larynx;

EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

M. M. Kennaway and E. L. Kennaway (1936) examined the death certificates of cases of cancer of the lung and of the larynx in males from England and Wales for 1921-32; there were 8808 cases of lung cancer, and 9472 cases of laryngeal cancer. The incidence of lung cancer in tobacco manufacturers was found to be 196, of laryngeal cancer 65; the incidence of lung cancer in tobacconists and their assistants was 175, of cancer of the larynx 142. In interesting contradistinction, those occupied in supplying alcohol showed a much higher incidence of laryngeal than of lung cancer.

It has often been noted that cough is a constant sign in many heavy smokers, especially cigarette-smokers (C. C. Rice, 1897; Fantus, 1936; R. B. Scott, 1952a, b; Myerson, 1953; Joules, 1954; W. C. Boake, reported in Lancet, Lond. *1:* 512, 1957; I. Gordon, 1957; among others).

According to Bogen (1937), it appears that smoking may lead to more frequent localization of tuberculosis involvement in the larynx. Statistical investigations were said to show a higher incidence of laryngeal lesions among tobacco-users, and clinicians repeatedly report that patients recover from this complication more readily if they abstain from smoking, although similar improvement is reported following the "silence" or laryngeal-rest treatment.

Ahlbom (1937) reported that tobacco was used by 86% of 312 male lip-cancer patients, while, in contrast, there was a 98% incidence of tobacco-use in 233 cases of the oral cavity, larynx, pharynx, and esophagus, as well as in 68 cases of buccal, gingival, and mandibular cancer. Of 132 women with cancer of the oral cavity, only 15% used tobacco; and among 113 women with cancer of the pharynx, larynx, or esophagus, tobacco appeared not to have played a role.

A number of observers have suggested, or found, that different modes of tobacco use are related to the development of cancer at one particular site. Of the 312 cases of lip cancer in men reported by Ahlbom (1937), 57% smoked pipes, 6% used cigars and cigarettes, 37% used snuff and chewing-tobacco (some obviously used more than one form). In contrast to this, of 233 male cases of cancer of the oral cavity, larynx, pharynx, and esophagus, 25% were pipe-smokers, 40% cigar- and cigarette-smokers, and 35% used snuff and chewing-tobacco. Of 68 cases of buccal, gingival, and mandibular cancer, 23% were pipe-smokers, 7% cigar- and cigarette-smokers and 70% used snuff and chewing-tobacco. Of 87 male cases of cancer of the pharynx, larynx, and esophagus, 20% used pipes, 64% cigars and cigarettes, and 16% snuff or chewing-tobacco.

In their book on the larynx and its diseases, Jackson and Jackson (1937, p. 378) presented this formulation of the cause of cancer:

$$A + S + C + I + F + a + T + H + xyz = E$$

where a = alcohol and T = tobacco.

EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

(of cough)

Jarvis (1938), on the other hand, considered the cause to be tobacco dust; he had cigarette dust counts made by a dust-count engineer, which enabled him to state that each time one inhales from a cigarette, one takes in 120,000 particles of dust 10 microns or under in size. Hence, smokers were said to present a mild dust problem, wherein dust might overload the lung lymphatics, and bring about cough. Application of the wet-filter principle (moistening of the mouth end of the cigarette with saliva for about one-fourth inch before lighting and starting to smoke it) was found to reduce the dust counts, develop a cool smoke, and result in disappearance of cigarette cough within 2 weeks in the majority of patients. Jarvis added: "If the cough does not markedly disappear in two weeks' time, one looks elsewhere for the source of the cough."

Hollis (1939) considered tobacco catarrh as a disease-entity which should be managed as such. He observed that in virtually all cases, the nasal membranes were less colored after smoking and the airways definitely more patent, and stated that a daily routine of these rapidly-changing phenomena repeated 20–40 times would, and undoubtedly did, cause chronic secretory changes, altered response of the mucous membranes to environmental changes, relaxation, and undue thickening of surface and sub-surface tissues, with shortness of breath, cough, and hoarseness. Three cases were presented in which laryngeal conditions cleared up upon abstinence from tobacco.

Hollis (1939) felt very certain that very many Americans who are constantly "out of voice" were suffering from a low-grade chronic hypertrophic laryngitis resulting from a so-called tobacco cough.

Hollis (1939) was inclined to believe that tobacco played a definite part in the production of contact ulcer of the larynx. In some 10 cases of this condition seen by him in smokers, simple voluntary aphonia was not sufficient to effect a permanent cure, and withdrawal of tobacco was necessary in order to bring about reasonably prompt recovery. Perhaps on the basis of this work, avoidance of tobacco was recommended in the treatment of contact ulcer of the larynx (J. A. M. A. *128:* 1259, 1945).

Jackson and Jackson (1939) considered it was the smoke, not the nicotine or the tobacco as it grows naturally, which constituted the irritative factor in the development of cancer of the larynx, and that it was the empyreumatic oil of tobacco produced in the destructive distillation of burning tobacco which was the essential irritating factor in tobacco-smoke.

Jackson and Jackson (1939) and Wallner (1954a, b) considered tobacco-smoke a large factor in the production of chronic laryngitis.

EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

1940 - 1949

In view of the relatively enormous increase in the use of smoking tobacco by women, and of the hitherto rare incidence of this disease in females, Jackson and Jackson (1941) remarked that it would be interesting to note the incidence of laryngeal cancer in women during the next decade.

Kaye (1942, 1944) reported that a high percentage of soldiers suffered from catarrh of the upper respiratory passages, and that this condition was aggravated by the excessive use of tobacco so prevalent in the army.

According to Podolsky (1943), "Oil in tobacco smoke is another suspected cause of" cancer of the throat.

W. Fischer (1943) considered it had not been proven that smoking plays a part in cancer of the larynx;

Regarding the mechanism of smoker's cough, M. F. Jones (1943) considered the condition to be a result of the effect of nicotine on the autonomic nervous system, resulting in altered secretions of the nose, pharynx, trachea, and bronchi. Cigarettes have a greater effect than cigars or pipes because inhaling increases the contact with the mucous surface through which the nicotine is absorbed.

According to Kaye (1944), the limitation of smoking for even 2 or 3 days will exert a beneficial effect upon smoker's cough. M. F. Jones (1943) considered the best remedy to be 6 weeks without tobacco.

In a series of 167 cases of cancer of the larynx reported by Mustakallio (1944), all but 2 were smokers, and 45 out of 100 of these cases smoked at least a pack of cigarettes a day. According to Clerk, Putney and O'Keefe (1948), a majority of 369 patients with carcinoma of the larynx used tobacco either moderately or excessively.

Potter and Tully (1945) analyzed information on the use of tobacco obtained from 2927 male clinic patients over the age of 40 in Massachusetts, and concluded there was a definite association between cancer of the buccal cavity and the use of tobacco, and that there also appeared to be some association between the use of tobacco and cancer of the respiratory tract. Cancer of the digestive tract, cancer of the skin, and cancer of all other sites was not related to smoking.

A. E. Hammond (1942) considered that the use of tobacco appeared to be a prominent contributing factor in cancer of the larynx;

Clerf, Putney and O'Keefe (1948) stated that nothing was shown to substantiate the belief that smoking was a predisposing factor. (for cancer of the larynx)

. Patients having smoker's cough usually show no abnormal physical signs in the chest (Gusterson, 1945)

a report by Heermann (1941) is interesting. This writer described the case of identical twins, in one of whom cancer of the vocal cords developed; and, since the one who developed cancer smoked, and the other did not, it was concluded that tobacco was the etiologic factor and, by inference, that a genetic predisposition was not present.

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EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

Schnur (1946) recorded 5 cases of patients who were moderate to heavy smokers (more than 1½ packs of cigarettes daily) and who had been coughing from 0.5–8 years; generally, the cough was non-productive and was exacerbated at night and in the morning. It developed that the cough was due to the use of tooth-powder, and eliminating its use diminished markedly or eliminated the cough in each of these patients without other therapy. Schnur's explanation was that the irritation of smoking raised the sensitivity of the mucous membrane of the pharynx, so that the small particles of tooth-powder which adhered to the posterior pharynx acted as an excitant sufficient to initiate the cough reflex. Such action was not allergic, but due to the irritation of an insoluble foreign body upon a hypersensitive membrane. The cough was aggravated immediately after brushing the teeth in the morning and evening, and was diminished during the day as the particles of grit were mechanically removed from the pharynx.

According to Fabricant (1946b), evidence of chronic pharyngitis, chronic laryngitis, and chronic tracheitis, characterized by symptoms of a sensation of rawness, sore throat, occasional hoarseness, and the production of laryngotracheal secretions, is found either individually or collectively in smokers who abuse tobacco. Such individuals can become free of symptoms by stopping smoking for a period of 5 weeks; conversely, they can reproduce their complaints by resuming smoking. In a general way, abuse can be defined only as that amount of smoking which would produce distress in the smoker's throat. Patients should be told to smoke within moderation, moderation depending on what the throat tells the smoker.

R. S. Stevenson (1947), discussing the throat in relation to singing and public speaking, stated that tobacco caused harm to the larynx by its local, not (as in the case of alcohol) by its systemic effect, the harmful agents being not nicotine so much as the burning of the chemical products by the destructive distillation of the tobacco. He suggested to singers with voice trouble that he himself would not personally smoke if he were a professional voice-user. If smoking were indulged in, the first third only of a cigarette was preferable.

Following an analysis of death certificates for cancer of the lung and cancer of the larynx in males from England and Wales for the years 1921–1938 inclusively, E. L. Kennaway and N. M. Kennaway (1947) stated: "Among various possible factors which have been suggested to account for the increase is tobacco smoking: the consumption of tobacco has risen, and so has the percentage of it smoked in the form of cigarettes, of which the smoke is often inhaled; such an effect of tobacco would accord well with the absence of social gradient."

When the occupational distribution of 139 patients with endolaryngeal cancer was compared with the occupational distribution in the Netherlands (1920 census), a large proportion were found to work in the "immaterial" professions, and few in the agrarian professions (Wassink, 1948).

H. Martin (1948, 1949) felt that, although excessive smoking with inhaling might be one of the etiologic factors in an occasional case of laryngeal cancer, smoking could not be shown to have a significant etiologic role in most cases of the disease.

According to H. Martin (1949), the addiction to tobacco among male patients with cancer of the tonsils is almost 100%.

EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

1950 - 1959

Myerson (1950) described a localized lesion of the vocal cord attributed to excessive smoking, and reported having seen the lesion in various stages in 143 patients, most of whom smoked 40 or more cigarettes daily. Histologically, this lesion was one of localized edema which becomes chronic, and as a result of chronic edema, fibrous connective tissue forms in the stroma, and an edematous fibroma results. Treatment is surgical, except in the early stage, when the lesion is purely edematous.

. In a series of 73 cases of cancer of the larynx and pharynx, Schrek and his associates (1950) found 69.9% cigarette-smokers, compared to 48.8% in a control group.

In a series of 73 cases of cancer of the larynx and pharynx, there were 69.9% cigarette-smokers, compared to 48.8% in a control group (Schrek *et al.*, 1950).

Moffett and McFarland (1950) pointed out that, in the past 10 years when more women had been smoking, and probably more of them drinking, there had not been any significant increase in incidence of laryngeal cancer in the female sex.

Moffett and McFarland (1950) considered that use of alcoholic beverages *per se* was not a significant etiologic factor of cancer.

G. Tucker (1935) and A. E. Hammond (1942) considered that vocal abuse appeared to be a predisposing or contributing cause in cancer of the larynx; but Moffett and McFarland (1950) thought not.

Moffett and McFarland (1950) considered that the etiology of the condition had not been established, but that smoking *per se* was not one of the significant etiologic factors of cancer. (cancer of larynx)

E. L. Kennaway and N. M. Kennaway (1951) also noted that, in spite of the increased consumption of tobacco, the incidence of laryngeal cancer in women had been stationary for the last 15 years, while the prevalence of cancer of the larynx in men appears to be decreasing.

Common experience, however, must recognize the existence of smoker's cough (R. B. Scott, 1952a, b), and many patients with this condition will get surprising relief on stopping smoking (Guerrant, 1951).

Grantham-Hill (1952) recorded having had a cigarette cough due to tracheitis, which disappeared after he began making and smoking his own cigarettes with rice paper.

R. B. Scott (1952a, b) stated that irritation from heavy smoking leads to chronic pharyngitis; but Myerson (1955b) remarked that the pharynx seems to be spared in a majority of smokers.

EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

A detailed account of smoking habits in 226 patients with malignant tumors of the larynx by Valko (1952) showed that 209 of 219 men smoked (188 were cigarette-smokers), while none of the 7 women in the series smoked. In a control group of 108 male patients of the same age-group with a diagnosis other than malignant tumor of the larynx, there were 77% smokers.

Deaths from lung cancer in males occurred in excess and at a relatively early age in England and Wales, compared to the United States; in contrast, deaths from cancer of the larynx and trachea occurred in excess and a relatively early age in America (Hewitt and Brooksbank, 1952).

In a series of 125 cases of keratosis of the larynx studied by Putney and O'Keefe (1953), 11.2% were said to be non-smokers. , they felt this figure might be significant when compared to the finding of 34% non-smokers in the survey of Mills and Porter (1950).

Kirchner and Malkin (1953) reported that, in a series of 235 cases of cancer of the larynx observed at New Haven Hospital over 30 years, 100 (43%) were classified as smoking excessively (over 1 pack a day) or chewing to excess; the authors noted that many more "moderate" smokers were not included.

Of 13 patients with carcinoma of the larynx, 7 were heavy smokers, 4 smoked moderately, and 2 were non-smokers (A. H. Miller and Fisher, 1953).

Some information concerning the relatively frequency of cancers in the various laryngeal regions is given by Friedberg and Wallner (1953). Of 31 cases of cordal carcinoma, all but one gave a history of smoking, and two-thirds smoked in excess of 1 pack per day; 19 of these revealed evidence of leukoplakia, and the majority of these patients were excessive smokers (2 packs or more a day). Of 18 patients with endolaryngeal carcinoma, all but 4 had a history of smoking; information as to smoking habits was not available for the remainder. Of 9 patients with subglottic carcinoma, 6 gave a history of heavy smoking; no smoking information was available for the other 3. Of 58 patients with extra-cordal carcinoma, 47 were habitual smokers, 9 were moderate smokers, and 2 were non-smokers.

Sadowsky, Gilliam and Cornfield (1953) found what they considered to be a real statistical association between cigarette-smoking and laryngeal cancer; in a series of 1990 cases of cancer of the lip, tongue, other oral-cavity sites, pharynx, esophagus, larynx, and lung, smoking histories showed that 91.9% of the patients smoked, compared to a 86.8% incidence of smoking in a control group of 615 patients with illnesses other than cancer.

In their statistical studies on smoking and cancer already described, Sadowsky, Gilliam and Cornfield (1953) observed no statistical association between pharyngeal cancer and smoking of any type:

The only specific reference to unburned tobacco in relation to laryngeal cancer appears to be by Kirchner and Malkin (1953), who reported that an unspecified number of their laryngeal-cancer patients chewed to excess.

EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

The sex differential for laryngeal cancer was reported by Dorn (1953a) to be greater than that for cancer of the lung and bronchus, the ratio of male to female morbidity rates being 10.6, or twice as large as for lung cancer. Male-female ratios in cases of cancer of the larynx reported by various authors bear out the sex-linked character of this disease: 20.5:1 (Valko, 1952); 37.7:1 (Friedberg and Wallner, 1953); 24.5:1 (Fusari, 1957); 6.8:1 (Montreuil, 1956).

Doll (1954a) noted that cancer of the larynx had, in the past, provided a good example of a type of cancer which was closely dependent on social conditions; but that the increasing gradient with descent in the social scale revealed in 1921–1923 is, however, now no longer apparent.

Baltzell and Putney (1954) surveyed 1498 cases of cancer of the larynx seen in the bronchoscopic clinic of Jefferson Hospital, Philadelphia, during 1928–1953. Of these, 186 (12%) were non-smokers, a figure which the authors compared to the 34% non-smokers in the general male population of Columbus, Ohio, as reported by Mills and Porter (1950). Regarding the smoking histories of the smokers, 249 patients smoked less than 1 pack of cigarettes daily, 563 smoked 1–2 packs, 152 smoked 2–3 packs, and 39 smoked more than 3 packs daily; 55 patients were moderate smokers of pipe and/or cigars, 62 were excessive smokers of pipe and/or cigars, and 82 were excessive smokers of pipe, cigars, and cigarettes; the smoking history of 110 patients was unknown.

Baltzell and Putney (1954) stated that, although more smokers were found in their series than in the normal population, this did not necessarily incriminate tobacco as an etiologic agent.

In the bronchoscopic clinic of Jefferson Hospital, Philadelphia, 84 cases of cancer of the larynx were seen during 1928–1933, 450 during 1934–1943, and 964 during 1944–1953; whether this increase was real and absolute could not be definitely answered by Baltzell and Putney (1954).

In an analysis of mortality from cancer of the larynx in the County Boroughs, Urban Districts, and Rural Districts of different parts of England and Wales for 1946–1949, Curwen, Kennaway and Kennaway (1954) showed that the Standard Mortality Ratio for cancer of the larynx in males increased with increasing urbanization, while cancer of the female larynx showed exactly the reverse relationship. From an analysis of the anatomical and sex distribution of 964 cases of cancer of the larynx, it appeared that this condition in men and in women are to a large extent different diseases, the so-called extrinsic group being more frequent in women.

Wallner (1954b) wrote that, although the etiology of cancer remained an enigma, chronic irritation was frequently listed [e.g. by Baltzell and Putney (1954)] as an important factor; and if one accepts smoking as an etiologic factor in keratosis, one must also regard it as a factor in the development of cancer of the larynx, since precancerous lesions are said to be important in the development of laryngeal carcinoma.

The cough is more marked in the morning (Joules, 1954), increases progressively with increasing cigarette consumption (A. M. Phillips, R. W. Phillips and Thompson, 1956) and with age (Joules; Phillips *et al.*)

EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

Ryan, McDonald and Devine (1955) compared microscopic sections from larynges from 3 non-smokers and 9 smokers, all of whom were men aged 40–60 years with no history of hoarseness or voice strain or recent complaints referable to the larynx, and who had died a relatively sudden death; they found (1) a thicker surface epithelium in smokers than in non-smokers, due in part to excess keratinization of the true cord, but mostly to epithelial hyperplasia at all three sites measured, namely, the false cord, the true cord, and the subglottic area; (2) a greater degree of round-cell infiltration in the smokers; (3) slightly more edema in the smokers; and (4) the presence of squamous-cell metaplasia in only the excessive smokers in this study. In a second study, a random series of 60 male subjects in the 40–60-year age-group was taken, and the foregoing criteria were used to designate the larynges as normal or not normal, "normal" being defined as the appearance of the larynx seen in the non-smoker in the pilot study. Smoking habits were ascertained following the study, and reliable information obtained on 40 of the cases. In 6 of 9 non-smokers, the epithelium was judged normal, while of 26 heavy or excessive smokers (16 or more cigarettes per day), 4 were judged to have normal-appearing epithelium. In the group of 5 light-to-moderate smokers, 3 were judged to have normal appearance, but 2 of these were cigar-smokers (who usually do not inhale). The authors concluded that this evidence supported the thesis that excessive smoking is associated with pathologic changes in the larynx.

In Blümlein's (1955) series of 241 cases of laryngeal cancer in males, 95.5% were heavy or very heavy smokers who habitually inhaled cigarette-smoke, and 87% had been cigarette-smokers for many years. In a control group of 200 cancer-free patients, heavy smokers amounted to only 9.3%; and there were 18% non-smokers compared to 0.8% non-smokers in the laryngeal-cancer group.

Blümlein (1955) maintained that there was a real increase in laryngeal cancer, and that the habit of cigarette-smoking alone could be held responsible for the increase in laryngeal cancer among the male sex. Other authorities, however, have noted that, in contrast to the increase in mortality due to cancer of the lung, the mortality due to cancer of the larynx has shown little change (Sadowsky, Gilliam and Cornfield, 1953; Curwen, Kennaway and Kennaway, 1954); and Doll (1955) wrote: "We need to know . . . why the association which appears to exist between cancer of the larynx and cigarette smoking has not been reflected in an increase in the incidence of cancer of the larynx comparable to that believed to have occurred with cancer of the lung."

In almost 400 edematous fibromas of the vocal cord, none has been known to undergo cancerous changes (Myerson, 1955a).

In a study of 4,580 individuals made by Ogden (1955), 7.3% of smokers complained of frequent coughs, compared to 2.6% of non-smokers; in this series, 60.2% of the men smoked and 26.4% of the women.

In a series of 100 consecutive cases of carcinoma of the larynx, the lesion occurred 3.5 times more often in those who smoked a pack or more of cigarettes a day than in non-smokers (Woodward, 1955).

EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

In the department of Antioquia, Colombia, Correa (1955) found 32 cases of cancer of the larynx in males and 17 in females, and he thought this large number of laryngeal-cancer cases in women might be related to the fact that, in Antioquia, many women smoke heavily and inhale the smoke. In some cases, the lesion has been found associated with the habit of smoking small cigars with the lighted end inserted into the mouth.

On the basis of tests on 18 physicians, Fishbein (1955) reported that changing to filter-tip cigarettes for 2 months resulted in a decrease in the amount of mucus in the throat and an accompanying disappearance of cough in most instances, and similar results were said to have been obtained on 24 other persons with cigarette cough.

One of the causes of elongation and hypertrophy of the uvula without acute inflammation may be the excessive use of tobacco over a long period of time (Kuyrkendall, 1955). Increased vascularity and firmness of the uvula has been observed in persons who have been smoking heavily for a long period of time (Myerson, 1955b). And, since smoking is said to influence the position and tone of the glossopharyngeal structures, excessive smoking was given as one of a large variety of conditions said to cause snoring (J. A. M. A. *144:* 886, 1950).

Sanghvi, Rao and Khanolkar (1955) questioned 1460 patients who attended the cancer clinic of the Tata Memorial Hospital in Bombay during 1952–1954 concerning their tobacco habits. Results of the statistical analysis were said to show that the habit of chewing was associated with cancer of the oral cavity; that the combined habit of smoking and chewing was associated with cancer of the hypopharynx and base of the tongue; and that smoking only was associated with cancer of the oropharynx and esophagus. Patients referred to the cancer clinic for a check-up, but who showed no evidence of neoplastic disease, comprised the "control group."

Lickint (1956b) suggested that the lower incidence of laryngeal cancers *versus* lung cancer may perhaps be due not to a lack of carcinogenicity of the tobacco-smoke, but to the fact that the tar dust cannot deposit permanently in the laryngeal mucosa so easily as in the deeper respiratory passages, and also possibly to the fact that the laryngeal mucosa has a greater resistance to carcinogens than does the bronchial mucosa.

Thomson and Schaff (1956) reported 5 cases, all in cigarette-smokers, of carcinoma of the larynx with concurrent or subsequent development of bronchial carcinoma.

All of a group of 70 patients with cancer of the larynx used to excess some form of tobacco (Montreuil, 1956).

Studies undertaken at the Sloan-Kettering Institute during 1954–1956 have shown a direct relationship between the amount of tobacco smoked, either in cigarettes, pipes, or cigars, and the risk of developing cancer of the larynx (Rhoades, 1954–1956).

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EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

Wynder, Bross and Day (1956) made epidemiological surveys of cancer of the larynx in America and in India. The American results were based on 209 male patients with cancer of the larynx, contrasted to 209 matched controls and with 132 male patients with cancer of the lung. Patients with cancer of the larynx included significantly more smokers than the matched controls; there was only 1 laryngeal-cancer patient who was a non-smoker, compared to 22 among the controls. The Indian data were based on 132 patients with cancer of the extrinsic larynx and 132 matched controls; 2 of the cancer patients neither smoked nor chewed, compared to 18 among the controls. The risk of developing cancer of the larynx was found to increase with both bidi-smoking and betel-nut chewing, with the risk of the former being the greater.

Wynder (1956) considered the evidence as good that tobacco is a causative agent in cancer of the lung and larynx and hypopharynx and oral cavity, and as fair it is related to cancer of the esophagus, and suggestive, but without particular evidence, in cancer of the stomach.

The relative risk of developing cancer of the larynx was also said by Wynder, Bross and Day (1956) to increase with the amount of tobacco consumed.

Other factors said to be related to cancer of the larynx include: edentia, hoarseness, and chronic cough (Wynder, Bross and Day, 1956), and exposure to strong heat during performance of work (Blümlein, 1957).

Wynder and his associates (1956) have reported some evidence that alcohol consumption increases a smoker's susceptibility to laryngeal cancer [Study Group of Smoking and Health (1957)].

Rhoades (1954–1956) implied that tobacco-smoking was a "promoting" factor in the disease.

N. M. Kennaway and E. L. Kennaway (1936), analyzing the incidence of cancer of the larynx in England and Wales for 1921–1932, found that those occupied in supplying alcohol showed a much higher incidence of laryngeal than of lung cancer. It is not certain that the previously observed association of this disease with alcohol persists (Doll, 1954a). However, the influence of heavy alcohol consumption as one of the environmental factors in laryngeal cancer has been emphasized (Rhoades, 1954–1956; Wynder, Bross and Day, 1956; Fior, 1957).

Pemberton and Macleod (1956) reported a survey of 642 men over 40 years of age living or working in 6 of 16 towns in the Nashoba Health District of Massachusetts, in which 28.8% were found to be either non-smokers or ex-smokers; 72 of the smokers reported having smoker's cough. A survey of 1,274 men by A. M. Phillips, R. W. Phillips and Thompson (1956) revealed an incidence of 34% of chronic cough;

EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

According to the information Hilding (1956d) had been able to glean from laryngologists, it would seem that 80–85% of all of the carcinomas occurring in the larynx occur in the cords, and the majority of these occur on the anterior portion or right at the anterior commissure. Hilding related these findings to ciliary streaming, thus: If carcinogenic substances of whatever nature (including cigarette-tar), which have been inhaled and deposited on the mucous blanket of the respiratory tract cause cancer in the larynx, it would likely occur first where the application of the substance to the epithelium is longest and most intimate. Experiments on ciliary streaming in human larynges removed at autopsy indicated that that region would be at the anterior commissure of the anterior portion of the cords, where the mucous blanket comes to a standstill, divides, and passes backward along the two cords. Although Hilding felt it possible that the characteristics of the ciliary streaming in this area might account for the distribution of carcinomas, he added that it could not be so concluded from present evidence. Other factors also were to be considered, such as the impact of air on the upper surface of the cords, air eddies, as well as a comparatively large amount of mucus which is being discharged from the ventricle over the anterior portion of the cords. Further experiments made it a reasonable assumption to Hilding (1957a, b) that, at the vocal cords in the living person, the mucous blanket is torn asunder to flow in two opposite directions at right angles to the previous flow; and the author pointed out again that carcinomas are apt to occur upon the vocal cords where the squamous epithelium acts as an obstruction to flow.

Passey (1957) described changes in the mucous glands and goblet cells of the respiratory epithelium of rats exposed to cigarette-smoke, with a concomitant increase in free mucus in the trachea and bronchi; and he suggested that this might be a counterpart of the condition in man resulting in smoker's cough.

Landes and McCabe (1957) reported the case of a 38-year-old woman who presented a curious manifestation of dysphonia, presumably on an hysterical basis. Exposed to an atmosphere containing cigarette-smoke, her voice dropped sharply in pitch and assumed a raspy, hoarse quality; examination of her vocal cords showed them to be quite normal both before and during the periods of hoarseness. On exposure to non-smoke-laden air, the return of the voice to normal was almost instantaneous. On testing with pipe-smoke, no change whatever in the quality of the voice occurred.

W. C. Boake (reported in Lancet, Lond. *1:* 512, 1957) confirmed the common impression that smokers coughed more, although they had no more sputum; they were said to have fewer sore throats, however—perhaps they had one all the time and did not notice it.

reference may be made to histological studies made by Michailow and Raitschew (1958) on the mucosa of the larynx of 100 smokers of both sexes in comparison with 10 non-smokers; the subjects were aged 40–70 years and had no indications of laryngeal disease. Smoking-related changes found were: thickening of the epithelium of the laryngeal mucosa; a more or less pronounced hyperkeratosis almost exclusively in the region of the true vocal cords; peculiarities of metaplasia of the cylindrical epithelium into a pavement epithelium. While these changes were not specific for tobacco, nevertheless the authors felt that they must be considered pre-carcinomatous if the individual has smoked cigarettes for a great number of years.

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EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

Wynder and his associates (1957) studied a group of 265 males and 207 females with squamous-cell cancer of the upper alimentary and respiratory tracts, collected at the Radiumhemmet, Stockholm, in comparison with a control group of 115 males and 218 females with various other types of cancers at other sites; tobacco consumption of the patients was also analyzed. The data on women were said to show a relation between smoking and gum and buccal cancer, but smoking could not account for the relatively high frequency of cancer of the upper alimentary tract in Swedish women. Among the male patients, a significant relationship to smoking was found for cancer of the lip (in pipe-smokers), tongue (in cigar-smokers), upper hypopharynx (in cigarette-smokers), larynx (in cigarette- and cigar-smokers), and esophagus (in cigarette- and cigar-smokers). Tobacco-chewing was found to be of suggestive importance only in cases of cancer of the buccal mucosa and of the gingiva.

Following a statistical survey in the North Wales and Liverpool region, Stocks (1957) reported that female hospital patients with lung cancer in Liverpool showed a significant excess of smokers, compared to the controls; but those with stomach and breast cancer in rural North Wales and Liverpool did not differ from the controls in respect to past smoking history. In men, pipe-smoking, which increases the risk of lung cancer only slightly, was associated positively in the Liverpool and Lancashire areas with the incidence of cancers of the larynx, esophagus, intestine, and rectum, and in Cheshire and Denbigh S. E. with cancers of the larynx, esophagus, and intestine other than the rectum. The percentage of cigar- and pipe-smokers among male patients with cancer of the oral cavity was found by Wynder and Bross (1957) to be higher than in a control group of patients, and the relative risk for these was calculated to be higher than for cigarette-smokers. More of the cancer group chewed tobacco, compared to the controls, but the tobacco-chewers were also (with one exception) smokers.

Schwartz and Denoix (1957) found a statistically significant correlation between cigarette-smokers and pulmonary cancer and upper aero-alimentary cancer, but not other cancers; pipe-smokers were negatively correlated with pulmonary cancer, not correlated with upper aero-alimentary or other cancers. Schwartz, Denoix and Anguera (1957) further studied the possibility of an association between tobacco and cancers of all locations in 2147 cancer patients, each with a non-cancerous patient and disease-free patient as controls of the same age (within 5 years), questioned on the same date by the same investigator in the same group of hospitals. An association was observed with cancer of the lung, buccal cavity, oropharynx, hypopharynx, esophagus, and, probably, bladder. Locations belonging to the upper aero-alimentary tracts were divided into two groups: the group of the respiratory type (lung, larynx), in which the tendency to inhale smoke and the predominant use of cigarettes were particularly marked; and the group of the digestive-tract type (buccal cavity, pharynx, esophagus), where the smokers' habit of rolling their own cigarettes was particularly marked, at least in the case of the buccal cavity and esophagus.

Fior (1957) felt that there might be important extrinsic factors (e.g. smoking and drinking) which, by acting on the larynx, might enhance the hereditary cancer potential already existing in such subjects.

EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

In a series of 170 patients suffering from cancer of the larynx, 81.24% were said to have been exposed, during a very long period, to a continual action of the environmental factors of smoking and drinking (Fior, 1957). In a series of 102 histologically proved cases of cancer of the larynx, 100 were habitual smokers, almost exclusively of cigarettes; 2 had never smoked (Fusari, 1957). Pipe-smoking was associated positively in the Liverpool, Lancashire, Cheshire, and Denbigh S. E. areas with the incidence of cancer of the larynx (Stocks, 1957).

it has been suggested that smoking plays some part or role, or has some influence on the development of laryngeal cancer (Hoffman, 1931; Fior, 1957; Fusari, 1957); and a statistical association or relationship has been found by a number of recent workers (Sadowsky, Gilliam and Cornfield, 1953; Rhoades, 1954–1956; Schwartz, Denoix and Anguera, 1957; Stocks, 1957; Wynder *et al.*, 1957; Hammond and Horn, 1958b). Sitbon and Hadida (1953) have reviewed the literature on the role of tobacco in the development of laryngeal and broncho-pulmonary cancers. More recently, E. Kennaway (1957) reviewed some of the studies which have been made on the etiology of cancer of the larynx, particularly in connection with the role of tobacco; and he reflected on some of the questions they raise.

Blümlein (1958) concluded that only one noxa, namely, tobacco-tar inhaled with cigarette-smoke, can specifically explain the increasing incidence of laryngeal carcinoma within the framework of an increasing frequency of lung cancer.

In the still-continuing prospective study by Hammond and Horn (1958b), an extremely high association of cigarette-smoking with cancer of the larynx was evident.

In a series of 59 patients with cancer of the hypopharynx, 26% were heavy smokers (Barbosa, cited in J. A. M. A. *168:* 802–803, 1958).

Sarma (1958) also reported a close correlation between the incidence of cancer of the larynx and the Assamese type of betel-nut-chewing habit; Assam is the easternmost state of India.

Wynder (1958) stated that in both laryngeal and oral-cavity cancer, the risk among cigar- and pipe-smokers of developing cancer in these regions was greater than their risk of developing lung cancer; and he presented data to indicate that, as one goes upward in the respiratory tract, the risk of developing cancer becomes greater for cigar- and pipe-smokers, while the cancer risk decreases for cigarette-smokers.

Wynder and coworkers (1958) also studied environmental factors in cancer of the respiratory tract in Cuba, based on 399 male and 107 female cases of cancer of the oral cavity, larynx, or lung, matched against controls. Whereas, in the male patients, 16% of the controls were non-smokers, only 1% of the laryngeal-cancer group were non-smokers; 42% of the larynx group admitted to smoking 35 cigarettes or the equivalent in cigars per day, in contrast to 29% for the controls. Cigarettes only were smoked by 49% of patients with cancer of the larynx; cigars only were smoked by 15% of the larynx group. In the females, there were 13% non-smokers in the larynx group, and 66% in the controls.

EXTRACTED FROM LARSON, HAAG AND SILVETTE (1961)

Wynder and Lemon (1958) reported preliminary findings on differences in incidence of cancers between 564 Seventh-Day Adventists and 8128 others (i.e. non-Seventh-Day Adventists), the point of the comparison being that only 6% of the Seventh-Day Adventists had a smoking history of more than 20 years, which compares to 85.4% in a sample of the general population. Thus, the smoking habits of the Seventh-Day Adventists males are similar to those of females in the general population; in addition, for all practical purposes, Seventh-Day Adventists are a non-drinking population. Epidermoid cancer of the lung was found to be 10 times less common among Seventh-Day Adventists than among the general population; actually, there was only 1 lung-cancer case in a Seventh-Day Adventist, and cancers of the mouth, larynx, and esophagus (previously shown to be related not only to smoking, but also to heavy drinking) were at least 10 times less common among Seventh-Day Adventists men than among men of the general population. All other types of cancer, with the exception of cancer of the bladder and cervix, occurred with the same frequency as in the general population; the latter occurred slightly less often than in the general population. These data and conclusions have been reported more fully by Wynder, Lemon and Bross (1959).

. an examination by Higgins (1957) of 331 men and 300 women, aged 25–74 years, in Wales showed that smokers of both sexes recorded a significantly higher prevalence of persistent cough and sputum than non-smokers; this was confirmed for Scotland and England (Higgins, 1958, 1959).

Analysis by Saslaw and Streitfeld (1959) of findings from 1812 throat swabbings showed that β-streptococci were isolated from the throats of present smokers almost twice as often as from non- or past smokers, a difference said to be statistically very significant ($p < 0.001$). Group A organisms were also isolated more frequently from smokers' throats, but this difference was not as statistically great ($p = < 0.05 > 0.02$). The higher frequency of streptococcal isolation among smokers than among non- and past smokers may be due to an effect of smoke products on streptococci or on the mucous-membrane barrier of the host. Antistreptolysin O studies (1611 samples) showed no appreciable difference in titers of sera from smokers compared to those from non-smokers.

According to Cracovaner (1959), hyperkeratotic lesions of the larynx are, in general, due to chronic irritation, among the sources of which is excessive smoking. Excessive smoking should be eliminated as part of the treatment of the condition.

Dutta-Choudhuri, Roy and Gupta (1959) ascertained tobacco habits in 582 patients with cancer of the larynx and hypopharynx, compared to those of 288 controls, from which they concluded that tobacco-smoking has a statistically significant role in the production of cancer of the larynx. Chewing tobacco did not similarly influence the incidence of cancer.

Stocks (1959) too stated that the risks of laryngeal cancer in men were increased in those who had been addicted to heavy cigarette-smoking.

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